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SCIENTIFIC OPENING OF THE WINNIPEG CHILDREN'S HOSPITAL

THE CHANGING ROLE OF THE CHILDREN'S HOSPITAL*

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IT IS SIGNIFICANT that the Board of Trustees and Staff of the Winnipeg Children's Hospital, who have brought this new modern hospital into being, are already looking into the future, and are concerned with the role it should play in the community in the years ahead.

Such vision of the people who feel responsible for the care of children in this part of Canada assures a continued growth of the hospital, and promises an institution which will continue to be sensitive to the needs of the times.

The well-known astronomer, Professor Harlow Shapley, has said, "Forecasting the future of the non-animate world is easy and can be made safely with a high degree of accuracy." For example, Shapley says, "I know where this planet will be at any required hour in the year 2000." But an accurate assessment of the changing role of hospitals which provide care for children is difficult, if not impossible. The character and function of any humane institution such as a hospital are determined by the nature of the period, and the qualities of the persons who establish them. Hospitals like events do not develop in a vacuum. Assumptions and current opinions have influence, and even these have environments and historical pasts which are significant. The relationship between hospital and society, which is a reciprocal one, is responsible for the changeableness of the hospital, and accounts for its dynamic qualities. Where a hospital does not respond to contemporary societal changes, it soon becomes inefficient and in time finds no reason to exist. Even the number of hospital beds needed cannot be predicted accurately by a formula, because that need will depend not only on the incidence and type of disease, but also on the habits of the physicians and the customs of the people—all of which are ever changing. It is reasonable to assume that the role of hospitals which care for children is particularly liable to shift because of the modifiable nature biologically of children themselves, and their ready receptivity to change under the influence of scientific and social endeavours which results in a decline of morbidity and mortality of childhood.

The difficulty of predicting the future role of hospitals should not deter us from making an attempt, however superficial, to gauge what lies ahead. As long as we are aware of the pitfalls in our analysis and leave room for correction of our errors, we shall remain true to the responsibility vested in us.

We are often told that understanding of the present, as well as prediction of future events, is possible if one searches the past. History may not *always* repeat itself, but it does so often enough to prove that lessons learned by review of the past frequently are helpful in forecasting things to come. This has been as true of general trends in medicine as in affairs of state. For example, lessons learned in times of war have been applicable in predicting and in helping to solve the problems of military strategy and of disease control in subsequent periods of warfare, and some benefits have been accrued for civilian populations in peace-time. The validity of mass psychological testing, as well as the success in group teaching by short-cut methods of education, in times of crises like the war years demonstrated how such activities may also be applied satisfactorily in work with citizens under other circumstances of life.

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Study of health trends and preventive medicine practices in one country has been useful in establishing similar projects in others. Industry and banking have used analytic methods to determine trends of business and consumer interest with great success and accuracy. It is this kind of review of the past and analysis of the present that I recommend to you now. I do this because at Yale University we have found that a study of the recent past has helped us project into the future. In order to do this objectively and scientifically we have turned to social scientists, particularly members of the Department of Sociology. It has been the experience of many that one can best become aware of *what has been* and of *what is going on* in one's community, by either leaving it for a while and then returning to it, or by inviting an outsider to come in and have a look. We have chosen the latter by asking sociologists to become members of the Department of Pediatrics for varying periods of time, in order to examine what has gone on in previous years. This has been part of the experiment at the University in collaboration of social scientists and physicians towards better understanding of the social, psychological and economic elements in the development of human illness, and the proper and adequate prevention and control of physical and mental pathology.

The experiments as applied to pædiatrics at Yale have consisted of three studies:

1. Sociologists under the direction of Professor August Hollingshead several years ago made a survey of the New Haven population in terms of social class structure. Out of this have come data which permit classification of the people residing there in the past ten years into five social classes. In addition, the information collected has provided insight into many activities such as marital practices, patterns of illness, and use of community resources such as hospitals and clinics. Against this background of data, studies relating to pædiatrics and the role of the pædiatric department at Yale were made. The first of these was carried out by Professor Albert Wessen. He undertook the task of finding answers to three questions: (1) What kinds of diseases require the admission of children to the hospital wards? (2) What are the results of hospitalization for various disease groups? (3) What is the age distribution of the population of the pædiatric ward; or putting it slightly differently, what is the expectancy of hospitalization for children at different age levels?

His study began with a survey of hospitalization data of the year 1944. At that time tabulation began to be made of all the cases treated in the wards according to major disease groups. The system of classification used was the topographic plan of the Standard Nomenclature of Diseases. Although there were some omissions in the data, as when some patients were not classified and when occasional errors in classification were made, there seemed to be a high degree of thoroughness and it is estimated that the error due to omissions of cases was less than 10%. It was believed that the clerical errors were not systematic and that the relationships found to exist could be considered substantially correct within normal limits of error.

The study concerned itself with the years 1944 through 1951. When all the diagnoses made over that period were ranked according to disease grouping, it was noted that the disease processes connected with the respiratory and nervous system accounted for almost half the total amount of diseases treated by the pædiatric service. However, the character of the afflictions which brought the patients to the hospital shifted; over the seven years of the study there was a steady lowering of admissions because of *acute* infectious diseases (except those of central nervous system), and an increased admission rate of so-called "chronic cases" of many kinds, but especially of the cardiovascular system. A steady decline of infections such as sepsis, ear and mastoid infections and lower respiratory disease was manifested. On the other hand there was a rise in the number of patients admitted because of poisoning, prematurity, and cardiovascular disease of the non-infectious type.

Attempts to evaluate the success of the hospital in dealing with disease is difficult. The traditional "signing out" of a patient at discharge with the clinical impression "improved" must be taken with a grain of salt. Too often it represents a note of optimism not founded on fact and represents more a wish fulfilment than either an accurate appraisal or a deliberate falsification to make hospital statistics look favourable to the institution. However, Professor Wessen's survey showed that from 1944 onward there was a real decline in mortality of children

in hospital because of ear and mastoid infections, exanthemata, and respiratory infections. Not only was there a lowering of the death rate, but children with these physical illnesses responded to treatment much more rapidly in this period than in the years before, so that the days spent in hospital were fewer.

Turning our attention now to the third question, namely the age distribution of the population of a pædiatric pavilion, the study confirmed clinical impressions that different diseases tend to strike persons of different age levels. About one-third of all the children admitted were less than one year of age. An approximately equal number were from one to five years of age, and the remainder were of school age. There were great variations in the extent to which diseases of different systems attacked children of the same age level. For example, 57% of all hospitalizations for gastro-intestinal disease took place among children under one year of age, while only 11% of the hospitalizations for infectious diseases of the central nervous system came from this age group. Grouping diseases which required admission to hospital by age groups gave the following results: In infancy, the largest number were gastro-intestinal diseases, congenital disorders, non-infectious central nervous system disease, infections of the skin, diseases of the eye and blood dyscrasias. In this age group there were also a large number of admissions because of difficulty of adjustment to feeding and sleep schedules. In the Standard Nomenclature these would be classified as conduct disorders, or in terms of clinical practice designated as psychophysiological problems or difficulties of parent-child relationship.

In the pre-school period, namely the age from two to five years, there was an increase in the number of infections of the central nervous system, diseases of the genito-urinary system, endocrine disorders, upper and lower respiratory infections, exanthemata with complications, sepsis and poisonings. The increasing mobility of the pre-school child removes him from the protection afforded him as an infant when he is not only isolated within part of a house but also separated from contacts with people from outside. As a crawler and toddler, the protective barriers disappear and his contacts with other people increase. This exposes him not only to sources of infection but to contacts with injurious and toxic substances. It is natural then that the plurality of hospital admissions among pre-school children should largely be infectious diseases and physical injury and poisoning. Seventy-two per cent of all children admitted to hospital because of poisoning due to ingestion of toxic substances were in the pre-school age group.

The school age period, that is children aged five years into early adolescence, showed increasing numbers admitted because of cardiovascular disease on a congenital basis which now seemed amenable to surgery. The number of children with rheumatic fever declined and Sydenham's chorea became almost non-existent. Diseases of the endocrine system, nervous system, bone, joint and muscle groups also brought school age children into the hospital for diagnosis and therapy. Children admitted because of so-called psychosomatic disorders, particularly ulcerative colitis, increased. One striking change has been seen after 1951 when Professor Wessen's survey ended—that is, the greatly reduced number of children admitted because of poliomyelitis.

The fact that almost equal numbers of infants, pre-school children, and school children were admitted to the Pediatric Clinic at the Grace—New Haven Hospital is in itself evidence of the extent to which young children are disproportionately subject to serious disease. The probability of admission to a hospital on the part of an infant is almost seven-and-a-half times as great as would be expected if hospital admissions were taken at random from the juvenile population of New Haven. For the pre-school group, this probability drops to 1.65 times what would be expected on the basis of chance, and in the school age period this drops off still further. So it is possible to compute the degree to which the incidence of hospitalization by ages for the different disease groupings departs from what would be expected if the juvenile population were affected by all diseases at random.

Professor Wessen concluded his appraisal with the caution to regard his findings not as dealing with morbidity *per se*, but with hospitalization at one medical centre. This centre unquestionably receives larger proportions of seriously ill children with knotty medical problems because it is a university clinic. For that reason, findings should not be taken as representative of an

average hospital. Furthermore, hospitalization itself is not an accurate index of morbidity, as has been demonstrated in the years since 1951 in our clinic when more children with upper respiratory infections have been treated at home, or as ambulant patients in our out-patient department. Very definitely illnesses which once were considered serious enough for hospital treatment, now may be managed better at home through the use of rapidly acting and specific drugs.

The findings of Professor Wessen (presented here greatly abbreviated) have been used since 1951 in planning the arrangement and distribution of hospital beds. For example, with the knowledge that infancy is the period of greatest vulnerability to disease which requires hospitalization, and is the period when congenital anomalies require hospitalization for diagnostic appraisal and surgical management, the number of beds allocated to infants, both medical and surgical patients, has increased. Similarly, the number of beds provided for children of any age who require surgical treatment has been increased. This is largely the result of the increasing success of cardiac surgery with congenital anomalies. The steady increase in the number of children requiring hospitalization not only for the diagnosis but for the treatment of acute crises in psychosomatic disease has warranted increasing the number of beds for older children and adolescents.

2. The second study that I would like to refer to briefly is that by Dr. Bert Brown of our resident staff. His interest has been a survey of the emergency room and the pædiatric out-patient department. In the five years from 1952 to the present time (1957) there has been an increase of 100% in the number of child-patients admitted there. This is a greater increase than that for the entire emergency room in our hospital for that period. As in the study previously reported, the greatest number were infants, particularly in the first year of life. There was a gradual decrease each year from infancy into adolescence. Fifty-nine per cent of the patients seen were under three years of age. By disease category, upper respiratory infections accounted for about 40% of the illnesses which necessitated coming for help. About 20% were lower respiratory infections, another 20% were exanthemata and rheumatic fever, and the rest made up a group of entities like gastro-intestinal disease, emergencies due to poison ingestion or physical injury, skin pathology and chronic recurring illness of various types. There were other findings relevant for us which need not be elaborated here; such as how the patients came to our emergency room, that is, whether referred by physicians or self-referred; racial groupings; economic background and the number who were sick enough to require hospitalization. This survey is helping us at the present time in expanding our physical plant to provide more examining rooms and waiting rooms in the out-patient clinic and in increasing the staff there.

3. A third study, which I will also mention very briefly, was that by Dr. Ray Elling on a sample of patients coming to the pædiatric-cardiac clinic. Dr. Elling was concerned with the problem of "co-operation of patients with physicians". For example, it had been noticed that some patients were very faithful in their clinic attendance and in carrying out the instructions of the physicians, particularly in the taking of penicillin as a prophylactic agent against rheumatic fever. Others only came irregularly to the clinic, broke their appointments frequently and were careless in their use of medications. Dr. Elling found a high positive correlation in terms of co-operativeness of patient with social class, and some interesting facts about the misconceptions and apprehensions which even co-operative patients have about their illness and its treatment. For example, patients who came regularly and were conscientious in their use of the medicines prescribed were those of Hollingshead's Social Class I—namely, those people who had more schooling, who took a greater part in the community affairs, who were better read, who attended church more frequently, and who were of the higher economic group. But even in this group there was frequently misunderstanding about how penicillin acted prophylactically. A fair number of these patients feared that penicillin made them impotent or sterile sexually. This led to their taking the drug with great anxiety. When more time was given to these patients in health education about their disease and the purpose of the various treatments, the anxiety was lessened if not relieved entirely, and made for a more happy acceptance of what before had been a handicapping existence.

There are other sources of information about changing trends in medical care in American communities which could be quoted. Not so long ago the American Hospital Association was asked to provide information to a children's hospital in New York City which was concerned with the decline in occupancy of hospital beds and which had the impression that sooner or later certain floors assigned to children should be closed or turned over to adult patients. The American Hospital Association made a survey of other children's hospitals in that area, including our hospital at New Haven. In each of eight or nine hospitals studied, there had been a yearly decrease in beds occupied over a period of several years. But while this was going on, in all but one of the hospitals surveyed there had been a dramatic and persistent increase in the number of patients cared for in the out-patient departments. You have probably seen reports of this nature, particularly in England, where not only has there been an increase in out-patient services but domiciliary care of greater proportions has been advocated. Lightwood[1] recently reported on a home-care program for sick children stemming from the St. Mary's Hospital Medical School and St. Mary's Hospital in London. He recommends domiciliary medicine for the humanitarian aspects, as well as for the advantage in providing greater continuity of medical care, since the patient not only feels comfortable when ministered to in his own home by his own parents, but is under the direction of the family physician while he is a bed patient as well as when he is ambulant or healthy. Although the bias for keeping children home was on the side of the less sick, seriously sick and especially incurable patients were also provided this care. The two groups best kept out of hospital were infants (33%) and toddlers (30%). Lightwood and others have also pointed out that the rising cost of hospitalization demands and forces parents to keep children out of hospital. I believe all of Lightwood's arguments are sound, and I am particularly struck with his demonstration, which has been the experience of others, that a domiciliary or home-care program has great educational value for a number of people. Like his countryman the late Sir James Spence, Lightwood sees home care as having teaching value to parents, not only in the educational sense, but in fostering a parent-child relationship which has tremendous psychotherapeutic benefit.

In this day when the American medical student graduates as a hospital-trained doctor, often having never set foot in the house of a sick patient, it is not unexpected to find him later as a practitioner of medicine overcome with feelings of uncertainty and anxiety when called upon to care for a patient in his own home. He becomes comfortable only when he can admit such a patient to a hospital, and have there not only 24-hour watching care and nursing, but also consultation from a number of colleagues. This has resulted in patients frequently being admitted to hospital who are not really sick enough to warrant that expensive measure. As I see it, the only way of giving the practitioner confidence in his ability to manage sick people in their homes is to give him that kind of supervised experience while he is a medical student and resident-in-training. A home-care program under competent senior staff supervision could bring this about. A home-care program which is carried on with the co-operation of the visiting nurse will not only assure better nursing care, but will also teach the physician-in-training about the helpful assistance of such a community resource.

I should like now to turn to a consideration of mental ill health. Physicians and lay people in our society are made very aware these days of the increasing number of children and adults who become sick with mental illness. Clinical investigation has emphasized many times that the origin of these illnesses frequently lies in infancy and early childhood. With a greater awareness of mental illness, it is not surprising that the diagnosis of infantile autism and juvenile schizophrenia, as well as psychosomatic disorders, is made more frequently today than ever before. Hospitalization is sought for these children, primarily for diagnosis because today we have little specific, scientifically determined treatment to give them, whether in hospital or on the outside. Children's hospitals are now faced with the problems of providing some beds for these patients. There is a strong temptation in those hospitals particularly where there is a decline in hospital bed usage, to convert some pavilions into residential treatment centres for emotionally disturbed children. Before this is done, warning should be given as to the great financial cost of this kind of medical care

and the difficulty of adequately providing such children with the emotional milieu which they need therapeutically. The ordinary pædiatric staff, even with some psychologic insight, is usually not trained well enough to cope with these children. In order to deal with them properly, psychiatric rather than pædiatric hospital services are needed. This is not to say that a close working relationship may not be worked out between pædiatricians and psychiatrists. When this is done, it unquestionably leads to better patient-care, and to greater learning by both pædiatricians and psychiatrists. I believe this is one of the important and interesting areas of further experimentation, just as in the past few years we have seen experiments in the teaching of medical psychology to pædiatricians, as necessary for the proper pædiatric care of children, whether it be in hospital or out-patient service. I am sometimes misunderstood in advocating a closer relationship between pædiatrics and psychiatry. To me the rapprochement of these two disciplines does not mean a subjugation of one to the other. I do not believe that the development of insight into human behaviour on the part of the pædiatrician, and the co-operative ministration of psychiatrists and pædiatricians to children in a hospital, means the giving up of the gains of traditional pædiatrics in the control of physical disease. I see no incompatibility between the development of modern pædiatrics, which emphasizes the whole child, and normal growth and development, and a continuation of the gains made in the past 50 years of pædiatrics in improvement of patient-care of children having physical illness. In fact, I am convinced that pædiatrics cannot develop further without psychiatry. In my use of the term psychiatry I am speaking broadly. I do not refer to psychiatric diagnostic procedures as applied to patients who are mentally sick, but rather to medical psychology, which helps one understand personality development, the meaning of behaviour and what disease and ill health connote as well as what they denote.

Understanding the emotional needs of children and their parents by physicians will in the future lead to greater change in procedures of hospital admission, and in the practices of patient-care once the child is in the hospital and subject to contact with many professional persons who represent a strange new world. It will, I believe, make us examine our present physical structures to see if they are of the greatest benefit psychologically to our patients, or whether they still follow architectural patterns set many years ago when they were established to provide greater convenience to the doctors, nurses and maintenance workers rather than for the comfort and convenience of the patients. As medical historians have pointed out, the first children's hospitals in Europe were fashioned after foundling hospitals. They were too frequently considered as refuge homes for slum children, and too little as places for the scientific study of diseases. Furthermore, architecturally they followed until recently the design of hospitals built for adults, which meant that they developed the same cheerless corridors, rooms that were isolated or wards in which one had little privacy. Standards of adult care were also followed where children were concerned in such matters as visiting hours and regularity of feeding, toileting and putting to sleep. The child has often been considered a miniature adult, as if he could take easily separation from parents. As a result he has on too many occasions been separated suddenly and completely for periods of days and weeks. In this time he has seen many persons, some who spoke to him cheerfully on occasion, but mostly others who were too busy being concerned with his physical care to consider him as someone craving social attention. Hospital staffs aware of the inhumaneness of this approach and of the psychological traumatic effects which frequently follow, are attempting to remedy such unhappy practices by setting flexible visiting hours, by encouraging parents to "live-in" with their child and participate in his care during some critical period of his illness, by keeping all channels of communication between hospital room and home open by even such a method as telephoning at bedtime in order to say goodnight to parents. Thinking of the feelings of the child when he is to undergo anæsthesia and surgery, and by providing auxiliary personnel to talk to the child, to listen to him, to play with him—all these are now recognized as important prophylactic measures in the reduction and prevention of immediate hospital psychologic reactions, and possibly even the prevention of serious long-term after-effects.

Mention has been made before of the importance of the out-patient department of a hospital. I would like to return to that with a few

remarks. It is my belief that the out-patient department constitutes an area of patient-care and diagnostic appraisal which demands the most skilled and experienced senior staff members, not only to direct it, but to serve as attending physicians. Like the physician in practice, and in fact to prepare medical students for that role, the clinician dealing with ambulant patients often must alone deal with problems without benefit of a galaxy of other staff members of higher or lower hierarchy who wait on him as super-specialists. While some consulation should be and is frequently available to members of the O.P.D. staff, the responsibility for providing watchful care while the patient is out in the community is usually borne alone, and this takes maturity and self-confidence. For this reason, I believe that the O.P.D. must be closely supervised and in the hands of capable persons, and should not be turned over to pædiatricians-in-training, who themselves are still trying to learn, and who too frequently know only patient management based on in-patient hospital training. While there is some need for specialty clinics in an out-patient service, I think there is too often the tendency to make a general pædiatric out-patient service merely a traffic agency or referral depot. Physicians working there as well as students-in-training soon find this uninteresting, because there is no opportunity to follow up their diagnostic or therapeutic efforts, and the incentive for thoroughness is lost. To remedy this, a general pædiatric clinic should keep as many of its patients there, for complete diagnostic study and treatment, with colleagues from special branches of medicine coming to this clinic as consultants so that the patient feels he has his own doctor who will guide him through all of the mazes of medical management. As in in-hospital treatment, out-patient therapy proceeds best when the care of each patient is supervised and controlled by one physician whom the patient considers his own special and responsible adviser, and who provides some main-thread of continuity over the days, months and years of care in that institution. There is an easy tendency to set up specialty groups for patients with certain diseases like cerebral palsy, mental retardation, nephrosis, blood dyscrasias and others. The separation of such clinics within the institution, or even apart from it in other geographic areas, is unsatisfactory, except for the single purpose of fund-raising by bringing attention of the public to its special needs. There is even a tendency today to think of rehabilitation as something separate and apart from other medical care. I refer specifically to the special rehabilitation clinics which very often provide only special physical therapy, and which overlook other physical and psychological needs of the patient. This is carrying fragmentation of a clinic to a point where patients' care is dangerously incomplete and impersonal.

A good pædiatric out-patient department may serve as an educational organization for the community in many ways. It has long been a place for physicians in the community to volunteer time in service. It has not provided enough opportunity for postgraduate education of the doctors in the community. It may serve them in a number of ways, by providing consultation services for their private patients, and by clinical conferences. One of the most successful and popular teaching exercises in our out-patient department at Yale is conducted by Dr. Albert Solnit. Each Thursday morning for an hour, he meets with a small number of physicians in practice to discuss their patients, when there are problems of personality development, behaviour or patient-physician relationship. This group teaching endeavour has provided consultation as well as general guidance in patient management.

Another potentially effective educational venture is that which includes a hospital service relationship with an elementary and secondary school or school system. This is not the time to discuss the deficiencies in most school health services. Suffice it to say that one reason for the inadequacies of such services is their isolation from organizations in a community, particularly medical and nursing agencies. A school physician and school nurse feel separated, even from other colleagues in the health department which may sponsor them, or in the school system of which they are a part administratively. Children referred by a school health official to a hospital out-patient department frequently do not receive benefit of such a referral because of the lack of communication between the physicians and nurses in both organizations. The report from the school physician to the hospital staff is meagre and incomplete, and the reasons for sending the patient for further study are not clear to the patient or his parent, and hence not to

the out-patient department physician who admits him. After more or less study, the child is referred back to his school, but communication again may be non-existent, or the report sent may have missed the point of the referral, and for that reason be inadequate. One way of overcoming these difficulties is to give pædiatricians-in-training experience in a school system working as school physicians. Another way is to have conferences in either the school or the out-patient department of all the persons involved in dealing with the problems of a specific child. In this way there may be collective pooling of information, and a making of decisions by group action which will be more acceptable, more practical, and potentially more helpful than if they were the expressions and suggestions of one person alone. The use of social workers in an out-patient department and social workers in a school system frequently facilitates the coming together of the staffs of the two institutions, and in the better carrying-out of a program set up for helping children.

Pædiatricians in practice as well as pædiatric educators have become very aware these days of the importance of emotional growth and development. Since much of their practice deals now with the healthy individual, and with problems of behaviour and learning, it is natural for them to want training and experience in developmental examinations, psychologic appraisal of children at all ages, and some understanding of modern methods of psychologic and personality testing. As a result, children's hospitals are developing clinics of child development for both training and research. Sometimes, like the Child Study Center at Yale, these are administratively separate institutions, but with a working relationship with a department of pædiatrics, and with staffs which work in both the children's hospital and the child study centre. There are many variations in the structure and function of these centres and institutes. In my experience, I have found it most practical and realistic to have members of our Child Study Center staff, such as pædiatricians particularly trained in developmental testing, child psychiatrists and clinical psychologists, work as members of our department of pædiatrics, see children on the wards and in the out-patient clinic and there demonstrate techniques to pædiatric residents-in-training as well as to staff members. By this manœuvre rather than having the residents-in-training rotate through the Child Study Center, we have tried to give the feeling that these areas of child study belong naturally within the framework of pædiatrics, and are not extraneous or impractical adjuncts possible only in a university setting. Since our goal is the preparation of physicians for practice outside of university and hospital settings, we have attempted to demonstrate how psychologic and developmental studies of patients may be made in a setting which is natural for a practising pædiatrician in terms of physical arrangement, and in a way which is practical within the time limits of scheduled private practice.

With the growing interest these days in the out-patient clinic and home care we are witnessing the completion of a cycle which began in 1769 in London, when Dr. George Armstrong opened the first "Dispensary for the Infants Poor".

Armstrong opposed the establishment of a "House Fitted up for the Reception of such Infants as are very ill" as had been done for adults in hospitals, on the grounds that such an infants' hospital would separate mothers and babies and lead to psychologic trauma. He probably also was influenced by the fact that, in hospital, infants readily picked up infections and often succumbed. Eighty-three years later the need for an in-patient hospital for children was recognized in England with the founding of the Great Ormond Street Hospital for Sick Children. The interest of the physicians in practice, in home care and in dispensaries and hospitals during the 18th and 19th centuries was primarily in sickness and in curative pædiatrics, because of the high rate of childhood diseases and death which prevailed during this time. However, in the 20th century the focus of pædiatric concern broadened to include the well-being of the healthy child as well as of the sick, and total rehabilitation instead of only recovery from disease.

This was partly the result of scientific discoveries which reduced in unbelievable measure morbidity and mortality of children, and of the change in philosophic concepts of the natural history of disease and the role played by environment. The relationship between cause and effect in disease is being viewed today less as a one-to-one relationship, and more as interrelationships and correlations of multiple factors. Concomitant causes are sought as well as single,

primary biologic agents. Modern psychiatry has stimulated all of medicine to view etiology multi-dimensionally. As a result, present-day pædiatrics is no longer concerned merely with the fact that a pathogenic organism produces an infection in a part of the body, but equally with the problems of the genetic inheritance of the patient, how he has lived, where he lived, and what his illness represents as maladaptation between his body and his environment.

In conclusion, I believe it is safe to assume that there will continue to be successful conquest of disease, despite the appearance of new illnesses and variations of the old. Preventive measures, new drugs and new surgical techniques will continue to be effective. The future trend in hospital activities is likely to be towards increasing out-patient diagnosis and treatment, and diminishing in-patient care, with the latter being predominantly concerned with the management of the chronically ill and with the patients requiring surgery. The work of the community hospital will extend into other health resources, such as well-child conferences and schools, and will include domiciliary medical care. As community health needs develop, the hospital services must meet them, and where the hospital fills these obligations it inevitably becomes a teaching centre. When it does this, and when it engages in research as well as clinical practice and teaching, a hospital not only keeps up to date, but it anticipates events and initiates trends.

It is my opinion that this is the place where the Winnipeg Children's Hospital is at the present time. Making the most of the present, you already are staking out your future.

REFERENCE

1. LIGHTWOOD, R. *et al.*: *Lancet*, 1: 313, 1957.

THE PÆDIATRICIANS OF RED LION SQUARE*

ALAN ROSS, M.D., *Montreal*

LONDON, like any large city, is dotted with squares and it is not surprising to find that many of these have developed their own history over the centuries. By the natural gravitation of men of similar interests, they have acquired importance in the history of an art or a political party or a profession.

Such is the case with Red Lion Square, a small area in the centre of Holborn, around which historical events seem to have gathered for a long time. For pædiatricians, Red Lion Square's importance and interest lie in the fact that in the eighteenth century five men, who made important contributions to the understanding and care of sick and well children, lived or worked in the Square or just around the corner from it. I have had the temerity to call them the Pædiatricians of Red Lion Square, though their training may have fallen a little short of certification requirements.

The Square was actually built in 1698, but the history of the spot goes back to Roman times, for one of the first Roman roads passed through its present site, a road that was used for 1000 years. We know little of its history through the years of the Great Plague and Great Fire, but the area was again in the news when, on the night of January 30, 1661, the body of Cromwell was exhumed at Westminster Abbey, carried to the Red Lion Inn and the next morning hanged on a gibbet in Red Lion Fields until sunset. Dr. Nicholas Barebone, the inventor of fire insurance, who built the Square, had been a supporter of Cromwell. On an obelisk he erected in its centre is inscribed in Latin, "The unfeeling gravestone of a very unfeeling person. Why are you staring at me, traveller? Go away." From this and other evidence it has been suspected that Cromwell's body may have been secretly buried there.

Aside from its medical association, which brings it before us today, Red Lion Square has been the home of a number of interesting people. After his miraculous escape from the scaffold at the time of the Restoration in 1660, John Milton lived "as closely as possible" in a house near what is now Red Lion Square. In 1791, Joseph Haydn lived there for a year while he wrote and conducted six symphonies. In 1826,

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Charles Lamb sat for his portrait by Henry Meyer, a resident of the Square. John Harrison, inventor of the chronometer, lived there as did T. Morris, the designer of the Morris chair. There is evidence that the Pretender, on secret visits to London, visited Dr. Samuel Johnson and others at the home of Dr. William King, another resident. The first umbrella in England is reported to have appeared in Red Lion Square, sported by the prominent social reformer, Jonas Hanway, Esq.

Fig. 1.—The Foundling Hospital, London, in the eighteenth century.

London in 1750 had a population of about half a million. It was, of course, the only big city in England, for the Industrial Revolution was hardly under way. The city was, for the most part, a seething mass of people crowded into the crudest of living conditions, judged by present-day standards. In the central part of town, along the river, the streets were narrow, crooked, unkept and unpaved. Sewage and slops ran eventually to the Thames in open drains, and unbelievable swarms of flies and hosts of vermin were evidently an accepted part of the city dwelling. There was no good plumbing, no good water supply. Back from the riverfront, houses were more substantial and streets a little wider. In residential areas, like Hampstead, stood some of the stately homes of England. But even here, water came from wells and sanitation depended upon the "night soil men".

The state of infant health was appalling and reflects the attitude of medical men and the public of the day. About 75% of all babies christened were dead before they reached five years of age and Gibbon writes that "the death of a newborn child before that of its parents . . . is a strictly probable event". The Bill of Christenings and Burials for the year 1741, about the time that four of our pædiatricians were starting practice, is interesting: in London alone, 8000 deaths from convulsions, 2000 from smallpox and as a measure of diagnostic acumen, 1500 from teething. Infanticide from neglect was common, for who would question such a form of death when all of Queen Anne's 18 children died in infancy.

There were two classes, the upper and the lower, and each looked after itself. It was only about mid-century that we see the first glimmer of a sense of responsibility of the more fortunate class for the health, and particularly the infant health, of those less favourably disposed. Here is the dawn of the Infant Welfare Movement, so well recorded by Dr. Ernest Caulfield of West Hartford, Conn. Early in its development, this movement was dramatized and given great impetus by the formal opening of the Foundling Hospital (Fig. 1) in 1740 under the enthusiastic patronage of "titled nobility and gentry more becoming to a coronation". The event was the culmination of 17 years of persistent effort on the part of the founder, Thomas Coram, a retired sea captain turned philanthropist and a stalwart character indeed.

Involved in this humanitarian effort with Coram was a resident of the Square, the man with the umbrella, John Hanway, Esq. He too had been a traveller, mostly in Persia and Russia. He made a fortune and retired to London at an early age. The rest of his life he devoted to social welfare and philanthropy of the most vigorous and practical sort. Eventually he was able to influence Parliament to pass the Infant Poor Laws of 1761 and 1767, which did away with many of the abuses practised in the disposal of illegitimate infants and decreed that infants in the care of the parishes should be cared for in the country for the first six years. His memorial can be seen in Westminster Abbey and he goes down in history as one of the great philanthropists and social reformers.

Medicine was passing through an interesting period in its development. Anatomy and physiology were beginning to be felt as strange forces in medical education, and chemistry, simple though it was, was being applied blindly to the treatment of patients. Pathology was just beginning to be related to clinical problems. Treatment was based upon "systems", profound philosophical theories, each explaining all diseases as due to one cause. Debate was intense, speculation rife.

But we are chiefly concerned today with five of London's practitioners who brought fame to the Square and enshrined it in pædiatric history through their concern with the problems of infants and children. Except for Walter Harris, they were contemporaries born between 1710 and 1720.

WALTER HARRIS

He was 50 years older and really belongs in the seventeenth century. His death is briefly recorded in *Gentleman's Magazine*, August 1, 1732, as "Dy'd Dr. Harris, a Physician in Red Lion Square". But by the profession he was not so casually dismissed, for his important work in Latin, "De Morbis Acutis Infantum", passed through 18 editions in a number of languages and three translations into English and was the recognized text in pædiatrics in England and on the continent for about 100 years. It commanded respect because it proclaimed a system. "All the causes of the disease of infants," he says, "spring from acid as their common source." There is nothing progressive about this but his pamphlet did contain some thoughts that were, at that time, revolutionary. He emphasized the importance of good history taking, including family history, for he recognized that certain diseases were inherited. "Let those who prefer a strong, vigorous and healthy offspring before money take care to avoid epileptic, scrophulous and leprous Mothers." He cautions against feeding infants "crude" meat for fear of worm infestation. "The languid Heat of old Men stands in need of spiritous Helps," he concedes, but he is against the administration of wine to infants. He recommends cheap domestic drugs and in his time was considered a therapeutic simplifier, though a favourite prescription, I note, was "Simple Powder of Crab's Claws, one Dram, Crab's Eyes, prepared, 2 scruples".

He was educated at Winchester School and New College, Oxford, was incorporated M.D. at Cambridge and was later made a Fellow of the College of Physicians. A fashionable and successful practitioner, physician to William III, a Censor of the College, Harveian Orator and Lumleian Lecturer for 22 years, it is little wonder that his teachings influenced medical thought throughout the eighteenth century. Much of his writing was expressly directed to the physicians who he says "go very unwillingly to take care of Diseases of Children" and it seems to me his real contribution was that he stirred up an interest in pædiatric problems at the turn of the century, an interest which, I like to think, directly stimulated the other four young pædiatricians who followed him in the Red Lion Square.

JAMES NELSON

James Nelson was 22 years old when Harris died and 34 when he moved to the Square. He practised in the same house for 50 years. He was an apothecary and proud of it, proud of the opportunities of seeing the patient early in his illness, before the physician was called in. One gets the impression of a warm, cheerful, kindly man. He raised seven children and was respected and loved by his patients. Although he had no university training or degree, he made a place for himself in pædiatric history by writing a most interesting little book, "An Essay on the Government of Children under Three General Heads, viz, Health, Manners and Education".

Under "Health" he writes with good sense about breast feeding and the introduction of solids. He cautions against giving tea to infants of any age and "strong malt liquor" to babies less than one year old. He agrees with his neighbour, Dr. Cadogan, that there is no indication for the practice of the day in which babies were strapped to frames to support the back and neck when being picked up.

He discusses the training of children in section two under "Manners". "By manners I do not mean that external Shew of Good Breeding, which consists only in a Bow or Curtsy or other personal Carriage, tho' this too is of Importance; but I mean such a Uniform Deportment, such a ready engaging Behaviour, and such a Propensity to what is right, as testify a happy Disposition of the Mind and Heart".

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And later on, "In the government of Children, Parents should set out upon right principles and then pursue them . . . never deceive their Children . . . avoid the Practice of Bribes . . . the Influence of Father and Mother should if possible be equal."

May I point out that this was written in 1753.

Fig. 2.—William Cadogan.

William Cadogan

Like Walter Harris, Cadogan (Fig. 2) was a distinguished London physician, educated at Oxford and Leyden. He too became a Fellow of the Royal Society and the Royal College of Physicians, a Censor and a Harveian Orator.

He is remembered for two thoughtful books written with force and sparkle: "A Dissertation on the Gout" and "An Essay upon Nursing and the Management of Children". In those days, of course, among the well-to-do, gout was a very common disease and Cadogan's book produced a storm of satire and criticism since he attributed the condition to "Indolence, Intemperance and Vexation" and prescribed activity, temperance and peace of mind. Reviewing it, Dr. Johnson said, "All that is good he stole, the nonesense is evidently his own."

His book on nursing was written because, he says, "almost half of the number of those who fill up that black list (The Bills of Mortality) die under five years of age" and it is reported to have revolutionized the care of infants of the period. It was the eighteenth century Spock, written originally as a handbook for the care of infants in the Foundling Hospital and its associated foster homes. A few quotations will show just how far back our pendulum is swinging.

"The truth is a new-born Child cannot well be too cool and loose in its dress; it wants less cloathing than a grown person in proportion and would bear the cold of a winter's night much better than any adult person whatever. There are many instances both ancient and modern of infants exposed and deserted that have lived several days."

"Shoes and stockings are needless encumbrances—they cannot be necessary till it runs out in the dirt."

"A child may be allowed any kind of mellow fruit—roots of all sorts and all the produce of the kitchen garden. At six or eight months they may by degrees be used to a little flesh meat."

"Nature, if she is not interrupted, will do the whole business perfectly well; and there seems to be nothing left for a nurse to do but to keep the child clean and sweet, to tumble and toss it about a good deal, play with it and keep it in a good humour."

Is it not too bad that so much of his teaching was forgotten in the years that followed?

John Fothergill

Dr. John Fothergill (Fig. 3) was the most distinguished of the lot. Actually he was probably the most distinguished physician in London and one of the best known characters of the English-speaking world in the 18th century.

Fothergill was a naturalist and like so many great physicians was keenly interested in everything that came within his line of vision. He was primarily fascinated by his patients and their diseases and rapidly developed an enormous and lucrative practice at a time when living was unbelievably cheap and yet a guinea was the standard fee. He was able to purchase a tract of garden ground in Essex which he developed into the only garden in England that rivaled the one at Kew. The most exotic plants

Fig. 3.—Dr. John Fothergill.

and trees were sent him by various friends and acquaintances all over the world. At one point, he sent a man to the African coast to collect plants, and many a sea captain assured himself of the services of the best consultant in England by filling his cabin, homeward bound, with specimens for Dr. Fothergill. Insects and shells and coral he collected and it was from the study of his coral that its animal origin was discovered by John Ellis.

A bachelor and a devout Quaker, he was the leading figure in the Society of Friends in England, with considerable influence among their fellows in Pennsylvania. He never visited America, but when Benjamin Franklin appeared in London with letters of recommendation from the Quakers of America, he found Fothergill thoroughly informed on, and sympathetic with the resentful colonists. The doctor threw the full weight of his influence in high places behind the visitor and together, for ten years, they laboured long and in vain to avoid the War of Independence. It was at meetings late into the night and around the breakfast table of "the house on Harpur Street, Red Lion Square" that they organized a campaign that almost turned the tide of history and certainly shows the versatility of these two extraordinary men.

Fothergill ranks as a pædiatrician because of his publications on a wide variety of diseases of children, for he was fascinated by growth wherever he saw it. His best known work is "An Account of the Sore Throat" that contains some delightful bits of clinical observation and description.

We see in what high regard he was held by his confreres from two memorial volumes that appeared after his death in 1780, but the tribute that appeals to me as the most genuine was a resolution by the Medical Society of London, "As the Doctor did not always write with the same felicity of style and weight of sentiment: this Society, from a true regard to his wishes and reputation as an Author, thinks it right to suppress some of his manuscript essays, which had been hastily conceived, and were too incorrect, and of a nature too light to obtain his own approbation."

GEORGE ARMSTRONG

I have left to the last the man who has been described as the father of modern pædiatrics.

George Armstrong was the son of the manse. Born in Scotland in 1719, he spent his life practising pædiatrics in London. By careful observation and by keeping meticulous records, he accumulated enough personal experience to publish, in 1767, a 148-page book titled "An Essay on the Diseases most Fatal to Infants to which is added Rules to be observed in the Nursing of Children with a particular view to those who are brought up by Hand." It influenced medical teaching well into the nineteenth century.

Appalled by the accepted wastage of life among the infants of London slums, he was able to interest enough prominent physicians and well-to-do sponsors to open a "Dispensary for The Infant Poor" at No. 7 Red Lion Square, the first pædiatric clinic in the world. He then proceeded to spend literally his last penny, a large part of his time and most of his energy treating the babies who were brought to the little dispensary. He preached against overfeeding, against swaddling, against the attributing of serious symptoms to teething. When he tried a new drug for whooping cough, he

Fig. 4.—George Armstrong's dispensary was situated in this house, No. 7 Red Lion Square.

divided his patients into two groups and compared the treated with the untreated. He diligently performed post-mortem examinations, describing the first pathological specimen of pyloric stenosis. Even the instruction of mothers in the care of their children and the prevention of disease was part of his day's work and it would appear that he probably taught other doctors, including foreign visitors.

We know that 35,000 infants visited the dispensary in the first 12 years of operation and though it moved twice in that time, the little house at No. 7 Red Lion Square marks the birthplace of the infant dispensary and clinic movement that soon spread throughout the world. Time has brought many changes. In the air raids of World War II, one-seventh of the Borough of Holborn was completely destroyed and three sides of the Square were laid waste. The old houses and rubble have been replaced by modern office buildings, but fortunately No. 7 and one or two houses on either side of it remain (Fig. 4)—a landmark in pædiatric history and really a memorial to the vision and devotion of George Armstrong.

Perhaps it has been bold to inject this discussion of medical history into a scientific program but it seems to me important to remember that the theme running through the whole recent growth and development of pædiatrics to a great extent was first developed in the eighteenth century by these five pædiatricians of Red Lion Square. Physicians and surgeons and investigators in many fields, here and elsewhere, have more and more elaborated upon this theme. And now, here in Winnipeg, life begins for this new Children's Hospital and work goes forward with these new facilities at a time when fundamental research is making rapid and important progress. I am sure that all of us predict for this centre a broad, free and adventurous future.

REFERENCES

1. CAULFIELD, E.: The infant welfare movement in the eighteenth century, Paul B. Hoeber, Inc., New York, 1931.
2. MALONEY, W. J.: George and John Armstrong of Castleton, two eighteenth-century medical pioneers, E. & S. Livingstone, Ltd., Edinburgh, 1954.
3. RUHRAH, J.: Pediatrics of the past: an anthology, Paul B. Hoeber, Inc., New York, 1925.
4. STILL, G. F.: The history of pædiatrics; the progress of the study of diseases of children up to the end of the XVIIIth century, Oxford University Press, London, 1931.

INFANTILE CORTICAL HYPEROSTOSIS

Infantile cortical hyperostosis, also known as Caffey's disease, is a pathological process characterized by localized enlargement of various bones due to hyperplasia of subperiosteal bone. The mandible and clavicles are most commonly involved, but the calvarium, ribs, scapulas, and long bones of the extremities may also be affected. As the most common symptoms are hyperirritability and fever, tenderness, dysphagia and pseudoparalysis, the disease may often be mistaken for other systemic disorders, particularly if the bone lesion is not obvious and is not the site of tenderness.

Morrison of Roswell, New Mexico, has recently reported a case in a female infant (*J. Pediat.*, 50: 487, 1957). The child was originally considered to be suffering from milk allergy. She had been placed on a soybean milk formula and improvement was reported. However, as infantile cortical hyperostosis is for the most part self-limited, this improvement was considered to be merely coincidental. Confirmation of this clinical impression was obtained when the child was put back on 1:1 evaporated milk formula without any ill effect. Her bone lesion is also subsiding. The author wonders whether or not a significant number of patients diagnosed as having colic, milk allergy and related conditions might not actually represent cases of infantile cortical hyperostosis.

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KERNICTERUS IN PREMATURES*

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It gives me great pleasure, on the occasion of the scientific opening of the Children's Hospital, Winnipeg, to bring you greetings and to wish you good fortune from your neighbour, the University of Saskatchewan. In addition, as a member of the British Pædiatric Association, I feel that my colleagues in the United Kingdom would like me on their behalf to bring you their greetings and good wishes for a successful and productive future in the field of pædiatrics.

YELLOW STAINING of the basal ganglia was first described by Orth in 1875[1] and the term "kernicterus" was coined later by Schmorl,[2] but for many years its etiology remained in doubt. With the discovery of the Rh factor by Landsteiner and Wiener[3] and the correlation of Rh incompatibility with hæmolytic disease of the newborn by Levine and his co-workers[4] it became apparent that kernicterus was a complication and in some respects the most important complication of Rh incompatibility, and that it was responsible for a large proportion of the deaths and for most if not all of the sequelæ in survivors. When it was realized that simple transfusions of Rh negative blood did not prevent kernicterus, a new approach became necessary and the technique of exchange transfusion via the umbilical vein was introduced by Diamond.[5] By 1950 he and his colleagues[6] were able to demonstrate conclusively that an early adequate exchange transfusion could virtually eliminate the development of kernicterus in babies with hæmolytic disease of the newborn, and reduce the incidence of kernicterus from approximately 33 to 1%. This work was confirmed in England by Mollison and Walker,[7] who also showed that prematures were more prone than full-term babies to develop kernicterus, i.e. that prematurity in itself was a predisposing factor.

The cause of kernicterus was initially in doubt. Some suggested that the brain damage was due to anoxia, others that it was due to the direct action of Rh antibodies on nerve cells, and still others that it was a secondary effect of liver damage, i.e. that it was a "hepatic encephalopathy". Hsia[8] and his colleagues, however, demonstrated that the incidence of kernicterus was closely related to the depth of jaundice in the baby, and that the higher the level of the serum bilirubin the greater the incidence of kernicterus. They observed that if the total serum bilirubin level remained below 20 mg. % kernicterus was rare but that when the levels rose to 30 mg. % or more, half the babies developed this complication. Once it was realized that it was the bilirubin level which was critical, exchange transfusions began to be employed on a wide scale; but no sooner did it appear that kernicterus had been eliminated than two groups of workers, one in Chicago[9] and the other in Bristol,[10] independently reported a series of cases of kernicterus in babies without hæmolytic disease, and it became apparent that neither Rh nor ABO incompatibility was essential to this disorder. We now know that although kernicterus is commonly associated with Rh incompatibility or ABO or other blood group incompatibilities, it may also be associated with the jaundice of prematurity, with congenital spherocytosis, with neonatal hepatitis and with familial non-hæmolytic jaundice.

A group of families with the latter condition have been extensively studied by Crigler and Najjar[11] and by Childs.[12] These children have an inborn error of metabolism and cannot convert indirect to direct reacting bilirubin; their indirect serum bilirubin level averages a little above 20 mg. %; kernicterus has developed in six of eight cases reported. These cases are of great clinical importance because in them it was first demonstrated that a high indirect reacting serum bilirubin, without any other complicating factors, could give rise to kernicterus. The importance of indirect reacting bilirubin was quickly confirmed by Claireaux and his colleagues,[13] who demonstrated that it was this pigment which was present in the kernicteric brain. Lathe,[14] a Canadian working in London, went on to show that, in the premature, the serum bilirubin level rises as long as liver function remains immature, because the immature liver cannot convert indirect into direct reacting pigment at the adult rate; in fact, in the very immature prematures the ability to do this may be only 1 to 2% of the normal.[15] There are therefore two overriding factors in the production of jaundice in the newborn: (1) hæmolysis; (2) the temporary inability of the liver to convert indirect into direct reacting pigment. These two factors are present in varying degree in every

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case of neonatal jaundice, and whenever the breakdown of hæmoglobin is excessive or the conversion of indirect reacting to direct reacting bilirubin is impaired the serum bilirubin level will rise and kernicterus may develop.

More recently Billing and Lathe[16] have shown, and Schmid[17] has confirmed, that the conversion of indirect to direct reacting bilirubin entails the addition of two molecules of glucuronic acid to the bilirubin molecule; this converts a relatively insoluble to a water-soluble compound which can be excreted by the liver. Arias and London[18] have shown that the enzyme responsible for this conversion utilizes the coenzyme uridine diphosphate glucuronic acid.

Although hæmolytic disease of the newborn is not the only precursor of kernicterus, can the association of the latter with prematurity be regarded as sufficiently common to warrant attention?

In Birmingham, England, I encountered[19] 91 cases of kernicterus associated for the most part with prematurity; none was due to hæmolytic disease. Sixty-three infants died in the neonatal period and the diagnosis was demonstrated at autopsy; 28 had survived the neonatal period and had varying degrees of choreo-athetosis with or without deafness. Those weighing more than 2000 g. at birth tended to survive. These cases were drawn from a large area, and the proportion of prematures likely to develop kernicterus is not necessarily high. At the Sorrento Premature Baby Unit, for example, where only the more immature prematures are admitted, 3.6% of all admissions developed kernicterus; the latter condition was found in 6% of necropsies. In Saskatoon at the University Hospital, there have been two cases of kernicterus among 99 prematures, an incidence of 2%; 21 of these prematures died, and kernicterus was therefore found in 10% of necropsies. At Winnipeg three cases of kernicterus were encountered in 114 autopsies undertaken on all infants dying neonatally and on stillborn fetuses during a 12-month period.[20] These three cases all occurred in prematures. Though it is not a common cause of death it is being encountered; it is moreover a disorder which can be prevented.

Crosse[21] and her colleagues have followed the serum indirect reacting bilirubin levels of both full-term and premature infants (Fig. 1). It is seen that the less the weight of the infant at birth the higher the subsequent bilirubin level and the later the peak. It takes six days, on the average, in the absence of any hæmolytic process to build up a dangerous level of bilirubin. This is in keeping with the observation that prematures most commonly develop kernicterus on the sixth day of life. Meyer[22] went on to study the indirect bilirubin levels of babies developing kernicterus. Two with this complication had levels below 18 mg. % and in the remaining 10 the levels were above 18 mg. %, but there were eight infants who had levels in excess of 18 mg. % and did not develop kernicterus. Two prematures developed kernicterus although the maximum serum bilirubin levels obtained were only 11.3 and 12 mg. % respectively; these weighed 907 g. and 1134 g. at birth. In Saskatoon a premature weighing 907 g. at birth developed kernicterus with a serum bilirubin of only 12 mg. %. It would seem that either the brain of the very immature premature infant is more susceptible to damage than that of its more mature counterpart, or that the blood brain barrier is more easily crossed in these cases.

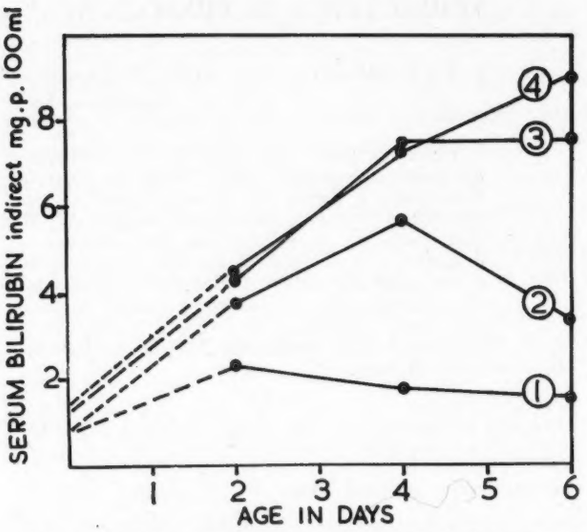

Fig. 1.—Indirect serum bilirubin levels in full-term and premature infants (modified from Crosse *et al.*[21]).
(1) birth weight 3500 g. or more (17 cases)
(2) birth weight 2500-3500 g. (29 cases)
(3) birth weight 2000-2500 g. (26 cases)
(4) birth weight up to 2000 g. (27 cases)

At the present time the only way to prevent kernicterus in prematures is by the removal of bilirubin by an exchange transfusion in selected cases. In suspected cases of hæmolytic disease of the newborn it is possible to foretell by an examination of the cord blood whether the baby will or will not need an exchange transfusion. By analogy, Meyer[22] wondered whether in prematures it might not be possible, by estimating

the serum bilirubin on the second day, to foretell which infant would develop kernicterus on the sixth. Unfortunately this did not prove to be the case, for he found later that though babies developing kernicterus had higher levels than normals on the second day (8.1 compared with 4.8 mg. % bilirubin) the majority of the babies whose levels were above 8 mg. % on the second day did not develop kernicterus. Prevention of kernicterus in these babies can therefore be carried out only by following up serum bilirubin levels from day to day, and giving exchange transfusions to those whose levels appear to be rising above 18 mg. %. An exchange of 60-80 ml. per lb. body weight is usually adequate. The umbilical vein can nearly always be used; blood of the same ABO and Rh group as the recipient should be used.

In this context it should be remembered that both menadiol sodium diphosphate (Synkavit)[23] and sulfisoxazole[24] have been shown to increase the depth of jaundice in prematures; the dose of the former should therefore be kept to a minimum, 1 to 2 mg., and the latter should be avoided.

I am grateful to my colleagues at the University Hospital for access to their cases.

REFERENCES

1. ORTH, J.: *Virchows Arch. path. Anat.*, **63**: 447, 1875.
2. SCHMORL, G.: *Verhandl. deutsch. path. Ges.*, **6**: 109, 1903.
3. LANDSTEINER, K. AND WIENER, A. S.: *Proc. Soc. Exper. Biol. & Med.*, 43: 223, 1940.
4. LEVINE, P., KATZIN, E. M. AND BURNHAM, L.: *J. A M. A.*, **116**: 825, 1941.
5. DIAMOND, L. K.: *Proc. Roy. Soc. Med.*, **40**: 546, 1947.
6. ALLEN, F. H., DIAMOND, L. K., AND VAUGHAN, V. C.: *Am. J. Dis. Child.*, **80**: 779, 1950.
7. MOLLISON, P. L. AND WALKER, W.: *Lancet*, **1**: 429, 1952.
8. HSIA, D. Y. Y. *et al.*: *New England J. Med.*, **247**: 668, 1952.
9. ZUELZER, W. W. AND MUDGETT, R. T.: *Pediatrics*, **6**: 452, 1950.
10. AIDIN, R., CORNER, B. AND TOVEY, G.: *Lancet*, **1**: 1153, 1950.
11. CRIGLER, J. F. AND NAJJAR, V. A.: *Pediatrics*, **10**: 169, 1952.
12. CHILDS, B. AND NAJJAR, V. A.: *Ibid.*, **18**: 369, 1956.
13. CLAIREAUX, A. E., COLE, P. G. AND LATHE, G. H.: *Lancet*, **2**: 1226, 1953.
14. LATHE, G. H.: *Brit. M. J.*, **1**: 192, 1955.
15. BILLING, B. H., COLE, P. G. AND LATHE, G. H.: *Brit. M. J.*, **2**: 1263, 1954.
16. BILLING, B. H. AND LATHE, G. H.: *Biochem. J.*, **63**: 6, 1956.
17. SCHMID, R.: *Science*, **124**: 76, 1956.
18. ARIAS, I. M. AND LONDON, I. M.: *Clin. Res. Proc.*, **5**: 213, 1957.
19. CLAIREAUX, A. E., GERRARD, J. W. AND MARSLAND, E. A.: *Rev. Int. d'Hépat.* **5**: 1153, 1955.
20. HOGG, G. R.: *Manitoba M. Rev.*, **35**: 575, 1955.
21. CROSSE, V. M., MEYER, T. C. AND GERRARD, J. W.: *Arch. Dis. Child.*, **30**: 501, 1954.
22. MEYER, T. C.: *Ibid.*, **31**: 75, 1956.
23. ALLISON, A. C.: *Lancet*, **1**: 669, 1955.
24. SILVERMAN, W. A. *et al.*: *Pediatrics*, **18**: 614, 1956.

RÉSUMÉ

Bien que l'ictère nucléaire ait été décrit en 1875, son étiologie ne fut comprise qu'avec la découverte du facteur Rh. En 1950 Diamond démontra d'une façon concluante qu'une exsanguinotransfusion précoce peut épargner l'atteinte aux noyaux gris centraux chez la plupart des nouveaux-nés souffrant de la maladie hémolytique. Il appartint à Hsia de démontrer que l'ictère nucléaire dépendait directement de l'intensité de la jaunisse et du taux de bilirubine du sérum. Il faut quand même se rendre à l'évidence que cet ictère peut aussi se produire dans toutes les formes de jaunisse qu'elle soit causée par la prématurité, la maladie hémolytique familiale, l'hépatite, etc. On a récemment démontré que le pigment biliaire incriminé dans cette affection est la bilirubine à réaction indirecte, de sorte que tout nouveau-né souffrant d'hémolyse ou de lésions hépatiques ne permettant pas la conversion de bilirubine "indirecte" en bilirubine "directe" est exposé à être atteint d'ictère nucléaire. On a observé que plus l'enfant est petit à sa naissance plus élevé sera le taux de bilirubine dans les premiers jours de vie et plus bas sera le seuil passé lequel apparaîtra l'ictère nucléaire. En pratique cependant, ce n'est que par des déterminations répétées du taux de bilirubine que l'on peut prévoir quel enfant en sera atteint et quel autre en sera exempt.

ORIGINAL ARTICLES

PRESENT STATUS OF POLIOMYELITIS VACCINATION*

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IT IS LITTLE MORE THAN four years since Dr. Jonas Salk[1] reported the first use of a preventive vaccine against paralytic poliomyelitis which he had prepared. The vaccine contained polioviruses of the three identified types, inactivated by formalin, and the observations were made on 161 children in Pittsburgh, U.S.A. It has been estimated that by May of this year (1957) more than 60 million persons in the United States and four million persons in Canada had received at least one dose of vaccine. The vaccine is in general use in Europe, South Africa, Australia, New Zealand and other countries. This is a development that is unique in medical history. Credit is due first to the National Foundation for Infantile Paralysis, New York, which since its organization in 1938 has generously supported research while providing treatment for every needy case of poliomyelitis in the United States. Among the

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recipients of assistance in research in 1951 was Dr. Salk of the University of Pittsburgh. Without the planning and support of the National Foundation, the evaluation of the vaccine which he prepared would have required many years. A field trial of a vaccine against poliomyelitis had to be planned on a very large scale and it was necessary that trial areas include representative sections of the whole country, since there is no way of foretelling in what part of the country the disease may be epidemic in any one year. The field trials conducted by the National Foundation in 1954 included 217 test areas in 44 states, two provinces of Canada, and Finland. In the United States approximately 1,830,000 children in the first three grades of school were kept under observation for the last six months of 1954. Of these about 440,000 had received, beginning in April, one or more injections of vaccine; about 210,000 received injections of a placebo; the remaining children, 1,180,000 were observed as controls. Blood samples were taken from about 40,000 children and the content of poliomyelitis antibody was determined before and after the injections of vaccine. This serological work was conducted in 27 laboratories. All data accumulated in the field trial were studied in an independent Polio Vaccine Evaluation Center established at the University of Michigan under the direction of Dr. Thomas Francis, Jr. This was the largest field trial ever undertaken, one of the most carefully planned and conducted, and one in which the results were evaluated in a minimum time. The findings were announced by Dr. Francis[2] at a scientific meeting at the University of Michigan on April 12, 1955. On the basis of the survey he reported that the vaccine was 80-90% effective against paralytic poliomyelitis, 60-70% effective against type 1 virus, and 90% or more effective against types 2 and 3.

CANADA'S CONTRIBUTION TO THE UNITED STATES FIELD TRIAL

This field trial depended on having sufficient vaccine, fully tested and available. Canada, through the Connaught Medical Research Laboratories, had an important part in this aspect of the trial. In speaking of this, Dr. Hart E. Van Riper,[3] then Director of the National Foundation, made reference to four contributions. The first was the contribution of Morgan, Morton and Parker[4] in 1950 in preparing a purely synthetic medium for maintaining animal cells in tissue culture. This medium, known as mixture No. 199, or a minor modification of it has been used by all manufacturers of the vaccine. A second contribution was the development in 1953 of methods for quantity production of polioviruses in cultures of monkey kidney tissue by Rhodes, Farrell, Wood, Franklin, Shimada and Macmorine.[5] A third contribution was the introduction of safeguarding tests, recognizing the possible presence of contaminating viruses derived from monkey kidney tissue, notably Virus B;[6] and a fourth, the actual production of more than 5000 litres of poliomyelitis virus culture fluids[7] for use in making vaccine. Of this amount, 3280 litres were made available to U.S. manufacturers who had undertaken to supply the vaccine. From this supply the bulk of the vaccine used in the field trial was prepared. Research work which led to the production of polioviruses in quantity, and the cost of the actual production of the large quantities of virus fluids, were made possible by the generous support of the National Foundation for Infantile Paralysis.

THE CANADIAN FIELD TRIAL

With the announcement of the plans for a field trial in the United States, the Dominion Council of Health, Canada, an advisory body composed of deputy ministers of health of the provinces and five other members, recommended to the Department of National Health and Welfare that plans be made to prepare the vaccine in Canada to permit a field trial in the following spring (1955). It was proposed that sufficient vaccine be prepared in the Connaught Laboratories to permit the administration of three doses to 500,000 children in the ten provinces. The plan was approved, the vaccine was prepared, and its administration was commenced on April 1, 1955, some days prior to the announcement of the results of the 1954 field trial in the United States. The cost of the vaccine used in this program and in subsequent programs conducted by the provincial and local departments of health has been shared equally by the Department of National Health and Welfare and the provinces.

Following the Francis report, immediate and nation-wide use of the vaccine was commenced

in the United States. Within three weeks, however, grave fears were expressed regarding the safety of the vaccine following a tragic occurrence of poliomyelitis among some of those who had received the first dose of vaccine; these children had received vaccine from one manufacturer. Additional cases were reported and the Surgeon General of the United States Public Health Service conducted a thorough investigation immediately. Temporary discontinuance of distribution of vaccine by all manufacturers was ordered until additional regulations relating to the preparation and testing of the vaccine were formulated and issued. A poliomyelitis vaccine surveillance program, established by the Public Health Service, required the reporting of all cases occurring among vaccinated persons. In all, 204 cases of paralytic poliomyelitis and 11 deaths were reported, 79 of which were among those receiving vaccine. One hundred and five were family contacts of these patients and 20 were community contacts. The work of this surveillance unit has been continued, and reports issued have indicated that the vaccine as prepared under the revised regulations has been entirely safe.

During the following six months, wide differences of opinion were expressed in the United States regarding the use of the vaccine. In Canada, however, the program was continued without interruption and with success. The original field trial in Canada planned for the administration of three doses to 500,000 children during the months of April, May and June, 1955. This number was increased as a result of the recommendation made by Dr. Salk, at the time that Dr. Francis presented his report, that the second dose be given one month after the first and that the third dose be administered not sooner than seven months after the second. The adoption of this recommendation in the Canadian program made possible the administration of the vaccine to 800,000 children in place of providing three doses for 500,000 children as originally planned. In two provinces, the original plan of three doses given at one-month intervals was followed.

PRODUCTION OF VACCINE IN CANADA

During the summer and fall of 1955 the Connaught Medical Research Laboratories, in common with other laboratories preparing the vaccine, encountered major technical difficulties which resulted in delay of the programs of vaccination as planned by the various provinces during the fall months. In November, further amendments were made to the regulations controlling vaccine production, and this created problems relating to the antigenicity or effectiveness of the vaccine. It was not until the late spring that vaccine production was again established in the Connaught Laboratories as routinely successful and quantities of vaccine were made available to the provincial departments of health for their program. In spite of these difficulties, sufficient vaccine was supplied during the spring months of 1956 to provide 2,200,000 doses. During the fall of 1956 and the first six months of this year regular supplies, more than 6,000,000 doses, have been furnished to the provincial departments of health. With the overcoming of problems associated with the presence of preservatives, the vaccine is now being distributed in multiple-dose, rubber-capped vials. These are more convenient for use in private practice. Preparation of the vaccine has also been undertaken in the Institute of Microbiology in the University of Montreal.

CANADA'S SATISFACTORY EXPERIENCE

The 1955 Canadian field trial was eminently successful. Through the Department of National Health and Welfare and the provincial departments of health, all data relating to poliomyelitis vaccination, including the investigation of every case of poliomyelitis occurring in a vaccinated person, have been collected and studied. Reports issued during the year 1956 have recorded that not one death from paralytic poliomyelitis occurred among the vaccinees.

The Department of Health and Welfare of British Columbia[8] was most helpful in analyzing the early results. During the period July 1 to November 30, 1955, 45,067 children aged 5, 6 and 7 years received two or three injections of vaccine. A total of 12,488 children in the same age groups did not accept the vaccine and these constituted a suitable control group for observation. Among the vaccinated children no cases of paralytic poliomyelitis were reported, whereas among the non-vaccinated children there were 10 cases of paralytic poliomyelitis.

The experience in Ontario in 1955 and 1956 is presented in a recent report[9] by the Department of Health, Ontario. During the spring months of 1955, 309,585 elementary school

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children in grades 1, 2 and 3 received two doses—approximately 90% of the children in these grades. The study group consisted of all children between the ages of 5 and 12 years, and the unvaccinated children in this group served as controls. Laboratory examination of stool specimens was conducted. In the 1955 study three cases of paralytic poliomyelitis occurred among the vaccinated and four among the non-vaccinated. During the spring of 1956 an additional number of children were vaccinated, bringing the total by July 1 to 840,000 elementary school children. During 1956 there were only five cases of paralytic poliomyelitis among the 840,000 vaccinated children in contrast to 71 cases among the 960,000 non-vaccinated children. The laboratory studies were of great interest. In 1955, of 62 illnesses reported as possible poliomyelitis 43 were finally classified as meningoencephalitis and of these 43 cases, 23 yielded on tissue culture examination a Coxsackie or an ECHO virus. In the 1956 study 180 cases were classified as meningoencephalitis and 103 yielded a cytopathogenic virus other than a poliomyelitis virus on tissue culture. It is necessary, therefore, that laboratory confirmation be obtained in all cases of non-paralytic poliomyelitis.

PREPARATION OF VACCINE

Poliomyelitis vaccine as currently prepared, following the method of Salk, is a suspension of three types of poliomyelitis virus, type 1 (Mahoney), type 2 (M.E.F.1) and type 3 (Saukett), grown in monkey kidney tissue in synthetic medium No. 199 and inactivated with formalin. The strains Brunhilde (type 1), Lansing (type 2) and Leon (type 3) were the archetypes used in establishing the types in 1951 but these strains were not used by Dr. Salk in preparing vaccine.

VIRUS CULTURE FLUIDS AND TESTS

The three strains (Mahoney, M.E.F.1 and Saukett) are grown in monkey kidney cells. With the exception of certain adapted strains, polioviruses will grow only in the tissue cells of primates; therefore, monkeys are used, and kidney tissue is employed as kidney cells permit a good growth of polioviruses. Healthy rhesus monkeys, tuberculin-negative, are anæsthetized and the kidneys removed aseptically. The animals are autopsied with special reference to the liver, spleen and lymph glands, and if any evidence of disease is found the kidneys are discarded. After removal of the capsules, the kidneys are minced, using scissors. After washing to remove blood serum, the minced tissue is added to large bottles[5] containing culture medium. The original medium No. 199 devised by Morgan, Morton and Parker contains amino acids, dextrose, vitamins and minerals—a total of some 60 ingredients—that have been shown necessary for optimal growth of cultured tissues. A minor modification of this medium is now used in vaccine production in the Connaught Laboratories. Penicillin, 200 units per c.c., and streptomycin 200 μg. per c.c., are added to the culture bottles to control possible bacterial contamination.

The culture bottles containing the minced kidney tissue are incubated for six days at 36° C. to allow the maximum growth of cells. The medium is replaced with fresh medium and the bottles are inoculated with one of the three strains of poliovirus. Penicillin is now being omitted from the medium used in this step, so that the vaccine distributed in the latter part of this year will contain only a minute quantity of penicillin. Incubation of the bottles containing cells and virus is continued for four to five days to allow the maximum of virus growth. Assays are made to determine the titre of the virus. Bacteriological tests, tests for the presence of contaminating viruses such as virus B, and assays of virus titres are made. Toxicity tests and tests for *M. tuberculosis* are made in animals. Virus fluids which do not meet all of these tests are discarded.

INACTIVATION OF VIRUS

The virus fluids are then filtered, using Seitz filters, to remove tissue-cell debris and to ensure bacteriological sterility. Filtration is a highly important step, as serious loss of virus will reduce the potency of the finished vaccine. The filtered virus fluids of the three strains are inactivated, separately, by adding formalin (1:4000) and holding the containers at 37° C. for a period of 12 days. During the first three days, virus assays are made to determine the rate of inactivation. At the end of seven days the vaccines are again filtered and incubation is continued for five days. This filtration has been added as a further safeguard in case some par-

ticulate matter might pass the first filtration or form subsequently, and might surround particles of virus, preventing their inactivation by formalin. Three days before the end of the inactivation, a minimum of 500 c.c. are tested in tissue culture for the presence of live virus. After the 12-day period of incubation a second test of equal volume is done. This test will reveal the presence of virus B or other simian viruses as well as polioviruses if present in these volumes. A preliminary test using monkeys is made to determine the antigenic value of the vaccine.

POOLING AND TESTING

When all tests are satisfactory, the vaccines of the three strains are pooled to form the trivalent vaccine. The formaldehyde is neutralized with sodium bisulphite, and a suitable preservative is added. The official antigenicity tests are made on the trivalent vaccine to confirm that the vaccine meets the antigenic standards. If the bacteriological tests are satisfactory, the vaccine is filled into sterile glass vials for clinical use. Bacteriological tests are made of the filled vials and tests are conducted to establish that there are no pyrogenic substances present. Confirmation of the safety of the triple vaccine is provided by testing 1500 c.c. of the filled vaccine in tissue cultures. In addition, a minimum of 20 monkeys are inoculated intracerebrally, intraspinally and intramuscularly with the vaccine. These monkeys are injected with cortisone to render them more susceptible to polioviruses and thus reveal the presence of any traces of living viruses. They are observed for 17-19 days and are then sacrificed. The central nervous system is examined for any lesions suggestive of poliomyelitis. Lastly, samples of the trivalent vaccine are sent to the Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, where the bacteriological, safety and antigenic tests are repeated. The vaccine is approved for use only if found satisfactory in both laboratories.

ADMINISTRATION

The experience on this continent has established that poliomyelitis vaccine (Salk) which meets the present government standards is entirely safe and that it is an effective agent in the prevention of paralytic poliomyelitis. The vaccine is clear and cherry-red in colour. Until recently, it was distributed by the Connaught Laboratories in sealed glass ampoules, since the usual preservatives were found to be injurious to the vaccine. This problem has been overcome and the vaccine is now being distributed in rubber-stoppered vials. If only part of the contents of a vial is removed, the air introduced into the vial may, on standing, cause the cherry-red colour to become a deep red shade owing to slight change in the alkalinity of the vaccine. Such vaccine is satisfactory for use, but any turbidity or sediment in the vial may indicate that the contents have become contaminated and the vial should be discarded. As previously mentioned, penicillin and streptomycin are added during the preparation of the vaccine, but only a very small amount of penicillin is present in the vaccine as distributed.

In regard to age, federal and provincial authorities urge that the vaccine be given to all persons under the age of 40 years. In the United States, last year there was a shifting of the highest incidence of paralysis from the age group five to nine years to the age group under five years, with the peak in the one to two year age group. From the age standpoint it is important to note that one-quarter of the cases with paralysis occur in adults. Pregnant women should receive the vaccine.

The vaccine may be administered subcutaneously or intramuscularly. It is recommended that three doses of 1 c.c. each be given, with an interval of four weeks between the first and second doses, and an interval of not less than seven months between the second and third doses.

If the series of injections be interrupted, it is not necessary to repeat the doses but simply to complete the series; an extension of the time interval between doses is not detrimental. It is of interest that even one dose of 1 c.c. appears to confer some measure of protection. It should be noted that the present evidence indicates that recall doses will be necessary to maintain protection and that these should be given after intervals of two or more years.

Is the administration of polio vaccine contraindicated during an epidemic of the disease? The possibility that the incidence of paralytic poliomyelitis might be higher and that paralysis might occur more frequently in the arm or leg in which hypodermic injections of various types were made has been carefully studied. On this

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continent, the consensus of opinion favours the carrying out of immunization during the summer months and in the presence of an epidemic of the disease. Polio vaccine was first used during an epidemic at the naval base in Hawaii in the fall of 1955. There was no evidence of an increased incidence of paralysis among the vaccinated. Poliomyelitis occurred as an epidemic in Chicago in August 1956; more than 1100 cases were reported, 75% of which were paralytic cases. It was decided to administer poliomyelitis vaccine to as many persons under 40 years of age as possible. More than 1,000,000 doses were given after the epidemic had commenced. It is of interest that not one case of paralytic poliomyelitis occurred in a person who had received three properly spaced doses of vaccine. Preliminary studies indicate that the occurrence of paralysis was not more frequent among the vaccinated than the unvaccinated. The vaccine was used also during an epidemic in Upstate New York in September, October and November of 1956, without incident. It is not considered that the use of the vaccine under such circumstances would materially affect the incidence of the disease; its value lies in providing protection against paralytic poliomyelitis on subsequent exposures.

REACTIONS

It is definitely established that the administration of poliomyelitis vaccine is remarkably free from reactions, local or general. Administration of many millions of doses of vaccine has established that reactions are very infrequent and generally of a mild nature. In administering vaccine to persons definitely known to be sensitive to penicillin or to the vaccine every precaution should be taken, including the use of a 1/10 c.c. initial dose given subcutaneously followed by gradually increasing doses. The possible occurrence of a severe reaction must always be remembered in administering hypodermically any product. It is desirable, therefore, to have epinephrine hydrochloride solution (1-1000) available as a safeguard.

CURRENT DEVELOPMENTS

Of great interest are the efforts to prepare vaccines containing attenuated living polioviruses in place of the inactivated virus vaccine now employed. Vaccination against smallpox with vaccinia virus, a living virus, brings to mind the advantages of a living virus vaccine, namely one inoculation and an extended period of protection. Yellow fever vaccine is another example of a living virus vaccine in which an attenuated strain of the virus is employed. It is recognized that recall or booster doses are necessary after a period of two or more years when vaccines prepared of killed bacteria or their products are used. The present polio vaccine (Salk), containing inactivated virus, requires the administration of three doses at intervals extending over a period of nine or more months and a recall dose will likely be needed after a period of two or three years. Insufficient time, however, has elapsed to permit a more definite statement.

Two groups of workers have developed attenuated living vaccines and preliminary clinical trials have been made. Koprowski[12] and his co-workers have developed a type 1 strain designated SM and type 2 strains TN and M.E.F.1. The strains TM and SM have been adapted to mice and are attenuated in that monkeys are not paralyzed after intracerebral inoculation. The SM strain (type 1) causes destruction of cells in tissue culture whereas TN does not do so. Both strains have been given to children in milk or in a capsule without any adverse result. These authors report that specific antibody formation was demonstrated in the majority of the children receiving the vaccine. Sabin[13, 14] has developed strains of all three types of polioviruses in tissue cultures which are non-pathogenic for monkeys when injected intracerebrally, although occasionally these strains have produced paralysis when injected intraspinally. Sabin has also isolated avirulent strains of types 2 and 3 from healthy children. In children after oral administration, and also after intramuscular inoculation, fæcal excretion of the virus occurs. In chimpanzees the attenuated strains of types 1 and 2 regained some virulence for monkeys. Recently, Sabin has reported further laboratory work which has suggested that there may have been a breeding out of virulent strains in the process of growth in the intestinal tract or on intramuscular injection.

Strains now being used appear to contain only attenuated virus. The question of safety of the attenuated or avirulent strains from the standpoint of their possible spread in the community

through excreta is receiving much attention. Reports of Dane and Dick[15, 16] of Belfast, Ireland, give grounds for concern. Employing strains TN and SM (Koprowski), these observers found that excretion of the virus in stools after the administration of the type 2 strain TN was irregular but that some individuals excreted virus for as long as a month and in high titre. The virus recovered from stools was pathogenic for monkeys when injected intracerebrally. More limited trials were made with SM virus. It was found that the virus recovered from vaccinated individuals was more virulent for monkeys than the vaccine strain, and was regularly present in the fæces, often in high titre and persisting for several weeks. From one individual, virus was isolated from the blood eight days after vaccination. In one family, infection of one child and possibly one adult was traced to contact in the home with a vaccinated child aged four years. It is possible that by improved laboratory procedures satisfactory avirulent strains may be developed. The method of pure culture of viruses developed by Dulbecco gives promise of important advances. Search is being made also for avirulent strains that may occur naturally. Another approach is an effort to breed harmless polioviruses in the laboratory by selective procedures. Cross-breeding of polioviruses is under study in an attempt to produce a single virus with the characteristics of the three known poliovirus types.

Improvements are being made in the preparation of the present vaccine. It is both difficult and costly to obtain the large number of monkeys required to provide the fresh kidney tissue used in propagating polioviruses for vaccine production. Dr. Salk recently announced that a strain of cells of monkey heart tissue, capable of continuous propagation, has been grown in his laboratory. These cells had remained susceptible to polioviruses and may prove to be satisfactory in the production of the polioviruses for vaccine. The use of this new cell strain would greatly reduce the number of monkeys required and also would remove the possibility that unknown viruses of monkey origin might be present in the vaccine.

PRESENT NEEDS

It is now known that vaccination protects against paralytic poliomyelitis but does not prevent intestinal infection with polioviruses. Vaccinated persons may still become carriers and may be the source of infection to others. The spread of infection of poliomyelitis would, therefore, be little affected by vaccination, and protection against paralytic poliomyelitis would be dependent on each individual's being vaccinated. In the control of diphtheria, however, through the use of diphtheria toxoid the disease disappears in communities when a sufficient number of children are protected, even though a considerable number remain unprotected.

When it is realized that approximately a quarter of all cases of paralytic poliomyelitis occur in the age group 20-40 years, the magnitude of the problem of poliomyelitis vaccination is appreciated. In Canada approximately 10,500,000 persons are included in the age group of infancy to 40 years; and since it is estimated that 4,000,000 persons have now received at least one dose of vaccine, there are 6,500,000 persons remaining to be given the opportunity of receiving vaccine. To meet this need the medical profession and the public health authorities should give leadership in a Canada-wide effort to provide vaccination. Every physician in his practice should urge vaccination of all persons under 40 years of age, emphasizing the safety, effectiveness and availability of the vaccine.

Another approach to this problem is the attempt to combine the present triple antigen (diphtheria, tetanus and whooping cough) with poliomyelitis vaccine. The advantages of such a quadruple vaccine are obvious. Because of the number of injections involved in giving protective vaccination against diphtheria, tetanus and whooping cough and against poliomyelitis, there is, already, a tendency to give only one series of inoculations and to omit either the triple vaccine or the poliomyelitis vaccine. The preparation of a quadruple vaccine was commenced in the Connaught Laboratories two years ago and the technical difficulties have been largely solved. The stability of the quadruple vaccine is now being determined, a procedure which requires extended testing and clinical trial. Similar work is in progress at the University of Michigan and at several other centres in the United States. A quadruple vaccine would be a most important contribution and would be welcomed by parents, physicians, and the administrative health authorities. Some physi-

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cians have given children both the triple vaccine and the poliomyelitis vaccine at each visit, injecting the triple vaccine and the poliomyelitis vaccine separately, in each arm. If the two antigens are mixed together in the syringe, injection should be made promptly, as the preservative present in the triple vaccine may reduce the antigenic value of the poliomyelitis vaccine.

SUMMARY

Polio vaccine in Canada has been established as entirely safe and studies confirm the findings that it is effective in reducing (75%) the incidence of paralytic poliomyelitis when three properly spaced injections are given. The recommended intervals are two to four weeks between the first and second doses and not less than seven months between the second and third doses. The indications are that recall doses will be necessary at intervals of several years.

Federal and provincial health authorities urge the vaccination of persons under 40 years of age, and all pregnant women.

Reactions due to the vaccine are uncommon and generally of a mild nature.

Adequate supplies of vaccine are available.

Vaccinated persons when exposed may harbour polioviruses in the intestinal tract and occasion widespread dissemination. Protection is dependent on each individual's being vaccinated.

Laboratory confirmation of diagnosis is urged in every case of poliomyelitis since a large number of non-paralytic cases are known to be caused by Coxsackie, ECHO and other viruses.

Although 4,000,000 persons in Canada have received at least one dose of vaccine, 6,500,000 persons under 40 years of age have not received any vaccine. To control paralytic poliomyelitis, the Canada-wide program of vaccination requires the support of every physician.

Encouraging progress is being made in the development of a quadruple vaccine (diphtheria, whooping cough, tetanus and poliomyelitis). Attenuated living virus vaccines continue to be the subject of important research.

REFERENCES

1. SALK, J. E.: *J. A. M. A.*, **151**: 1081, 1953.
2. FRANCIS, T., JR. *et al.*: *Am. J. Pub. Health*, **45**: No. 5, part 2, 1955.
3. VAN RIPER, H. E.: *Canad. J. Pub. Health*, **46**: 425, 1955.
4. MORGAN, J. F., MORTON, H. J. AND PARKER, R. C.: *Proc. Soc. Exper. Biol. & Med.*, **73**: 1, 1950.
5. FARRELL, L. N. *et al.*: *Canad. J. Pub. Health*, **44**: 273, 1953.
6. WOOD, W. AND SHIMADA, F. T.: *Ibid.*, **45**: 509, 1954.
7. FARRELL, L. N. *et al.*: *Ibid.*, **46**: 265, 1955.
8. TAYLOR, J. A., ELLIOT, G. R. F. AND NELSON, A. J.: *Ibid.*, **47**: 49, 1956.
9. ONTARIO DEPARTMENT OF HEALTH: *Ontario M. Rev.*, **24**: 259, 1957.
10. BROWN, G. C. AND SMITH, D. C.: *J. A. M. A.* **161**: 399, 1956.
11. BUNDESEN, H. N. *et al.*: *Ibid.*, **163**: 1604, 1957.
12. KOPROWSKI, H. *et al.*: *Ibid.*, **160**: 954, 1956.
13. SABIN, A. B., HENNESSEN, W. A. AND WINSSER, J.: *J. Exper. Med.*, **99**: 551, 1954.
14. SABIN, A. B.: *Science*, **123**: 1151, 1956.
15. DANE, D. S. *et al.*: *Brit. M. J.*, **1**: 59, 1957.
16. DICK, G. W. A. *et al.*: *Ibid.*, **1**: 65, 1957.

RÉSUMÉ

La vaccination contre la poliomyélite au Canada s'est révélée comme un procédé entièrement sûr. L'étude des résultats a démontré qu'une série de trois injections administrées à intervalles déterminés avait abaissé la fréquence de cette affection de 75%. Les intervalles recommandés sont de deux à quatre semaines entre la première et la seconde dose, et pas moins de sept mois entre la seconde et la troisième. Une dose de rappel deviendra probablement nécessaire après plusieurs années. Les autorités d'hygiène fédérale et provinciale recommendent la vaccination de toute personne âgée de moins de 40 ans ainsi que de toute femme enceinte. Les réactions qui suivent la vaccination sont rares et habituellement de peu d'importance. On possède maintenant des quantités de vaccin suffisantes pour les besoins de l'heure. Les sujets vaccinés lorsqu'ils sont exposés à la poliomyélite peuvent héberger dans leurs voies gastro-intestinales des virus qui pourraient répandre la contagion. Il est donc important que chaque individu soit vacciné. On doit obtenir la confirmation du diagnostic de la poliomyélite par des épreuves de laboratoire, car il est établi qu'un grand nombre d'infections non paralytiques peuvent être causées par les virus Coxsackie, ECHO et autres. Bien que quatre millions de personnes au Canada aient déjà reçu une dose de vaccin, six millions cinq cent mille autres personnes au dessous de 40 ans restent encore à vacciner. Afin de juguler les atteintes paralytiques de la poliomyélite, le programme de vaccination à travers le Canada exige l'appui de chaque médecin. Des progrès encourageants ont été réalisés dans le développement d'un vaccin quadruple (diphtérie, coqueluche, tétanos et polio), et des travaux importants sont en cours sur l'emploi de virus vivants mais atténués comme source d'immunité.

A STUDY OF DIAGNOSTIC ERRORS

Eleven hundred and six autopsies from one hospital, representing the period 1947 to 1953, were reviewed by Gruver *et al.* (*Ann. Int. Med.*, 47: 108, 1957), and an incidence of 6% incorrect clinical diagnoses was found. Infections, particularly pneumonia and meningitis, were the most commonly overlooked diagnoses. Other frequently missed diagnoses were neoplasms, especially of the liver and brain, surgical conditions of the abdomen, and cardiovascular catastrophes.

Forty-five per cent of the patients in this group were unable to give a history because of acute alcoholism, confusion or toxicity, shock, coma or aphasia.

Correctable diagnostic errors seemed to be due not so much to lack of medical knowledge as to deficiencies of medical judgment, alertness and thoroughness. These included failure to: (a) obtain routine screening tests; (b) investigate abnormal symptoms, signs or laboratory reports that did not fit in with the diagnostic impression; (c) pursue indicated procedures; (d) recognize new illnesses developing in the presence of a previously diagnosed chronic disease; (e) realize that x-ray examination occasionally may fail to disclose pathologic changes, and (f) periodically review the record in prolonged illnesses and repeat the physical examination.

COMPARISON OF THE EFFECTS OF PROMAZINE* AND CHLORPROMAZINE IN MENTAL SYNDROMES

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THE PURPOSE of this communication is to report on the gross clinical changes produced by promazine and chlorpromazine in mental disorders.

Since the introduction of chlorpromazine[1-3] into psychiatric therapeutics many attempts have been made to find substances similar to this drug but less toxic. Studies in acute alcoholic psychopathology[4, 5] indicated that promazine, a precursor of chlorpromazine, might fulfil such an expectation. In a previous study[6] promazine appeared to be similar in many respects to chlorpromazine in varieties of mental syndromes. The present investigation was undertaken to compare somewhat more systematically the effects of the two drugs in psychiatric cases.

MATERIALS AND METHOD

Promazine and chlorpromazine were administered to a total of 259 patients divided into three categories:

1. The first group consisted of 200 non-selected patients in an open psychiatric setting, or from an out-patient clinic, manifesting acute or recently apparent psychiatric syndromes. The first 100 patients received chlorpromazine in an average daily dose of 200 mg., for an average period of three to four weeks. The second 100 patients received promazine in an average daily dose of 300 mg. for an average period of four weeks. Except for five patients, the drugs were administered orally. The sex distribution in the two groups was similar and consisted of 65% female and 35% male patients, with an average age of 40 years. The syndrome distribution for the chlorpromazine group consisted of 28 cases of schizophrenia, 25 of manic-depressive states, 44 of neurotic states and 3 of organic psychoses; and for the promazine group, 23 cases of schizophrenia, 29 of manic-depressive states, 45 of neurotic states, and 3 of organic psychoses.

2. The second group consisted of 30 patients with the same characteristics as the first group, who received chlorpromazine and promazine in two different periods for the purpose of comparing the effects of two drugs in the same individual. In 13 cases of this group the switch from chlorpromazine to promazine was made because side-effects appeared. The group as a whole consisted of nine schizophrenics, seven manic-depressives and 14 neurotics.

3. The third group consisted of 29 male chronic schizophrenics from a closed psychiatric setting, with an average age of 38 years. They received chlorpromazine and promazine in two different periods for an average of three months.

The following investigations were performed on the patients of the first and second group: determination of blood pressure, pulse and temperature twice daily; weekly weight determination and urine analysis; white blood cell count and differential count once a week on the 50 cases of group (1); liver function tests consisting of plasma alkaline phosphatase, blood cholesterol and cephalin cholesterol fluctuation tests twice a week on the first 25 patients of the promazine treated group, and alkaline phosphatase determinations alone, twice weekly, for all patients. The reason for twice weekly determination of alkaline phosphatase was that in a previous study[7] it had proven a useful early indicator of liver damage in chlorpromazine-treated cases.

The degree of clinical improvement was recorded according to four criteria: (1) better ward management; (2) subjective relief of symptoms; (3) ability to live at home; and (4) ability to work. The patients were categorized as slightly, moderately, or markedly improved, according to whether they could be classified under criterion 2, 3, or 4.

RESULTS

1. *Physiological changes.*—The following differences were noted between cases treated with promazine and chlorpromazine. Promazine had a mild and chlorpromazine a moderate hypotensive effect. With promazine, blood pressure fell in 70% of patients; systolic blood pressure dropped an average of 10 mm. Hg, and diastolic pressure an average of 7 mm. Hg within 48 hours. Thirty per cent of cases showed no change in blood pressure. With chlorpromazine, blood pressure fell in all cases; systolic pressure dropped an average of 25 mm. Hg, and diastolic pressure an average of 15 mm. Hg within 24 hours. A relative circulatory collapse, in the standing position, occurred in one promazine-treated case and in 10 chlorpromazine-treated cases. There was an increase in appetite and a moderate gain in weight in about 60% of patients in both groups. The blood cell findings remained within normal limits under both drugs, except for an unexplained, uncomplicated moderate monocytosis in five chlorpromazine-treated patients. Liver function tests showed changes in 4% of promazine-treated patients, and in 25%

*Promazine under the trade name of Sparine was provided by John Wyeth & Brother (Canada) Limited, and chlorpromazine under the trade name of Largactil by Poulenc Limited (Canada).

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of chlorpromazine-treated cases. There were no detectable changes in urinary function. The barbiturate-potentiating effect of promazine was found to be similar to that of chlorpromazine. This conclusion was reached in comparing patients receiving prolonged sleep treatment with the method previously described.[8] One patient treated with promazine developed a marked sensitivity to insulin.

phrenics treated with an average daily dose of 400 mg. chlorpromazine, for a period of three to four weeks. There was a relatively identical result in improvement ratings in both instances, particularly in agitated, tense and anxious patients (10 in each drug category). In three cases an acute hallucinatory psychotic state disappeared. The main difference between the two drugs appeared to be in the intensity of

TABLE I.—COMPARISON OF EFFECTS OF PROMAZINE AND CHLORPROMAZINE IN SIMILAR CLINICAL SYNDROMES

Diagnosis	*No. of cases*		*Marked*		*Moderate*		*Improvement Slight or nil*	
	P	*C*	*P*	*C*	*P*	*C*	*P*	*C*
Schizophrenias	23	28	9	5	9	11	5	17
Manic-depressive psychosis	29	25	6	4	10	7	12	14
Neuroses	45	44	0	4	17	16	28	24
Organic psychoses	3	3	0	0	2	1	0	1
Total	100	100	15%	13%	38%	28%	47%	59%

P—Promazine. C—Chlorpromazine.

2. *Clinical changes.*—A brief account of the results obtained in each group, according to diagnostic categories, will be given.

1. *Group 1.*—One hundred chlorpromazine-treated cases compared with 100 promazine-treated cases. Table I gives the comparative effects of the two drugs according to broad diagnostic categories, and Table II according to sub-groups.

Schizophrenic states.—Twenty-three schizophrenics were treated with an average daily dose of 500 mg. promazine, and 28 schizo-

dosage and the time lag between the administration of the drugs and the onset of clinical response, both being greater with promazine.

Manic-depressive states.—Twenty-nine manic-depressive patients were treated with an average daily dose of 900 mg. of promazine, and 25 manic-depressives were treated with an average daily dose of 500 mg., for an average period of three weeks. The degree of clinical improvement was comparable with both drugs. Of 10 manic patients treated with promazine, six showed marked, three moderate, and one slight

TABLE II.—COMPARISON OF EFFECTS OF PROMAZINE AND CHLORPROMAZINE IN SIMILAR CLINICAL SYNDROMES

Diagnosis	*No. of cases*		*Marked*		*Improvement Moderate*		*Slight*		*None*	
	P	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*
1. Schizophrenias.										
Paranoid agit	10	10	5	5	5	5				
Paranoid non-agit	5	15			2				3	15
Hebephrenia	2	3			1				1	3
Borderline	6		4		1		1			
2. Manic-depressive psychosis.										
Manic	10	5	6	3	3		1	2		
Depression agit.	8	5		1	6	4	2			
Depression, non-agit.	11	15			1	1		2	10	12
3. Neuroses.										
Anxiety neuroses	23	27		4	12	12	9		2	11
Anxiety hysteria	6				1		3		2	
Hysteria	4	5					1	1	3	4
Obsession	3	5							3	5
Addiction	6	4			4	4	1		1	
Character neuroses	3	3							3	3
4. Organic psychoses	2	3			1	2	1			1
Post-lobotomy agit.	1				1					
Total	100	100	15%	13%	38%	28%	19%	5%	28%	54%

P—Promazine. C—Chlorpromazine.

improvement; of five patients treated with chlorpromazine, three showed marked improvement and two slight improvement. Of eight agitated depressed patients treated with promazine, six improved moderately and two slightly; and of five such patients treated with chlorpromazine one improved markedly and four moderately. The results in depressive states without agitation were equivocal. Here too the dosage and the time lag were greater with promazine.

Neurotic states.—Forty-five neurotics were treated with an average daily dose of 300 mg. promazine, and 44 neurotics were treated with an average daily dose of 200 mg. chlorpromazine, for an average period of four weeks. The improvement response was relatively similar, although four patients suffering from anxiety states showed marked improvement with chlorpromazine, and no case of marked improvement in anxiety states was seen with promazine. Hysterical and obsessive-compulsive patients and those with a character neurosis failed to respond to both drugs. Four out of six cases of addiction in the promazine group, and four in the chlorpromazine group, responded favourably in their initial post-withdrawal states associated with agitation and anxiety.

Organic states.—Three patients with organic psychopathological states in each drug group and overt symptoms of agitation, destructive outbursts, etc., showed considerable improvement in these aspects of their behaviour.

2. *Group 2* consisted of 30 cases of varieties of mental syndromes (Table III) receiving both drugs: chlorpromazine followed by promazine. In 13 cases this shift had become necessary because of the appearance of side effects. In the remaining 17 cases the shift was instituted voluntarily in order to observe the differential responses. The results, as seen in Table III, were quite similar with both drugs, particularly in manic patients and agitated paranoids. In these cases chlorpromazine was discontinued for two to seven days to see whether the manic or agitated paranoid state would return, and then promazine therapy was instituted. Manic cases, where the acute symptoms did not return or where the return of symptoms was not marked, were not included in the series.

The previous observation about the higher dosage of promazine and its longer time lag was quite evident in this group.

TABLE III.—COMPARISON OF EFFECTS OF PROMAZINE AND CHLORPROMAZINE IN THE SAME PATIENTS

Diagnosis	*No. of cases*	*Improvement*							
		Marked		*Moderate*		*Slight*		*Nil*	
		P	*C*	*P*	*C*	*P*	*C*	*P*	*C*
1. Schizophrenias.									
Paranoid, agit	3	1	1	2	2				
Paranoid, non-agit	4			1		2	2	1	2
Borderline	2	2			2				
2. Manic-depressive psychosis.									
Manic	2	2	2						
Depression	5					2	1	3	4
3. Neuroses.									
Anxiety state	7				2	4	2	3	3
Hysteria	1							1	1
Obsession	1							1	1
Addiction	2							2	2
Character neuroses	3					1		2	3
Total	30	5	3	3	6	9	5	13	16

P—Promazine. C—Chlorpromazine.

3. *Group 3* consisted of 29 chronic schizophrenics in a closed psychiatric setting, 15 of whom had shown moderate improvement in ward behaviour after two months of chlorpromazine therapy, with an average daily dose of 500 mg. In all these patients chlorpromazine was discontinued, and promazine therapy was substituted for a period of three months. Fourteen cases among the 15 previously ameliorated cases gave the same response with promazine. However, the dose of promazine had to be increased by about 200-300 mg. per day in order to obtain the same clinical response as with chlorpromazine.

SIDE EFFECTS

Table IV summarizes the percentage of different complications with both drugs. It should

be noted that in a previous study with chlorpromazine,[3] where routine liver function studies were not done, the incidence of jaundice was about 5%. In a subsequent investigation[7] the alkaline phosphatase level in plasma was found to be a reliable early index of hepatic dysfunction in chlorpromazine-treated cases. Since we began twice-weekly alkaline phosphatase determination we have had no cases of jaundice. In the present study the incidence of the rise in alkaline phosphatase was about six times greater with chlorpromazine-treated cases than with promazine-treated ones. With cessation of the drugs, alkaline phosphatase levels returned to normal in all cases. In one promazine-treated case, blood cholesterol rose abnormally and remained abnormal throughout the treatment with no other additional changes.

comatose with 10 units of insulin, though previously he had needed about 60 units to become barely somnolent. There were no alterations in the blood cells and no urinary changes.

We were impressed particularly by the lack of drowsiness and feelings of being knocked-out during promazine therapy, irrespective of clinical response. In the promazine-treated group only nine patients complained of undue drowsiness, while the incidence in the chlorpromazine group was about 50%. As mentioned, three patients who developed incapacitating drowsiness with chlorpromazine (100 mg. daily), when switched to promazine (200 mg. daily) did not show this state though the clinical response was identical. In manic patients the improvement in ward behaviour occurred with much less sleepiness, fatigue and inactivity with promazine than with chlorpromazine. It was observed that in out-patients or privately treated cases this relative absence of drowsiness and knocked-out feeling was an advantage, in that it allowed the patients to continue their social activities or work with little discomfort.

TABLE IV.—COMPARISON OF SIDE EFFECTS OF PROMAZINE AND CHLORPROMAZINE

	Skin reactions	*Oedema*	*Extrapyramidal symptoms*	*A P rise*	*Epilepsy*	*Collapse*
Promazine	4%	4%	0	4%	0.08%	10%
Chlorpromazine	6%	6%	4%	25%	0.01%	1%

A P—Alkaline phosphatase.

In Group 2, treated with chlorpromazine sequentially, 13 cases developed serious or uncomfortable side effects, necessitating a change of drug. These side effects consisted in five cases of a rise in plasma alkaline phosphatase (once associated with a rise in serum cholesterol), in four of a dermatitis (one with œdema), in three of an incapacitating drowsiness, and in one of an epileptic seizure. Under promazine therapy in the dosage mentioned above, the clinical response was identical, but all side effects disappeared except in one case. This patient, who had shown a rise in plasma alkaline phosphatase with chlorpromazine, manifested a decrease in this reaction but developed a sudden transitory rise in temperature; this, however, did not necessitate the discontinuation of promazine.

One chronic schizophrenic in Group 3 had an epileptic seizure two days after the administration of chlorpromazine. He had another epileptic seizure on the second day of promazine therapy. The incidence of extrapyramidal syndromes was 4% with chlorpromazine and nil with promazine. One patient who was receiving somnolent insulin and was put on promazine manifested a marked sensitivity to insulin and became sub-

SUMMARY AND CONCLUSIONS

The foregoing data, based upon gross clinical observations on 259 patients, leave the following impressions of the comparative effects of promazine and chlorpromazine:

1. Promazine and chlorpromazine have a similar effect on the overt behaviour and symptoms of patients with mental disorders.
2. To obtain this similar clinical response the daily dosage of promazine should be from 30 to 100 mg. higher (per dose) than chlorpromazine in acute or recently appearing psychiatric cases, and from 100 to 400 mg. (per dose) higher in chronic psychiatric cases.
3. There is a greater time lag between the administration of the drug and the clinical response to promazine than to chlorpromazine. This time lag seems to be about 24-48 hours with oral administration of the drug. With intramuscular or intravenous administration this time lag seems to be non-existent.
4. Regardless of the clinical response, promazine produces much less drowsiness and knocked-out feeling than chlorpromazine.

5. There is a relative absence of liver dysfunction, as assessed by the tests used in this study, with promazine (4%) in comparison with chlorpromazine (25%).

6. Extrapyramidal complications occur in about 4% of chlorpromazine-treated cases, but not with promazine.

7. A shift from chlorpromazine to promazine can be instituted if serious complications occur with the former substance without their reappearance with the latter drug.

8. The impression was reached that the therapeutic locale par excellence for promazine is the outpatient clinic and private practice, where the appearance of complications and undue drowsiness is socially and individually more important.

REFERENCES

1. DELAY, J., DENIKER, P. AND HARL, J. M.: *Am. med. psychol, Paris*, 110: 267, 1952.
2. LEHMANN, H. E. AND HANRAHAN, G. E.: *A.M.A. Arch. Neurol. Psychiat.*, 71: 227, 1954.
3. AZIMA, H. AND OGLE, W.: *Canad. M. A. J.*, 71: 116, 1954.
4. FAZEKAS, J. F. *et al.*: *J. A. M. A.*, 161: 46, 1956.
5. MITCHELL, E. H.: *Ibid.*, 161: 44, 1956.
6. AZIMA, H. AND DUROST, H.: *Canad. M. A. J.*, 76: 442, 1957.
7. STACEY, C. H. *et al.*: *Ibid.*, 73: 386, 1955.
8. AZIMA, H.: *J. Ment. Sc.*, 101: 593, 1955.

RÉSUMÉ

Les auteurs de cet article ont cherché à comparer les effets de la promazine et de la chlorpromazine telles qu'administrées à une série de 259 malades. Ces deux produits agissent de la même manière sur le comportement et les symptômes des malades mentaux. Il faut cependant augmenter chaque dose de promazine de 30 à 100 mgs dans les désordres psychiatriques aigus ou d'origine récente, et de 100 à 400 mgs dans les cas chroniques par rapport à la dose de chlorpromazine qui suffirait dans les circonstances. Les effets de la promazine ne se font sentir qu'après 24-48 heures lorsqu'elle est administrée oralement. Les deux produits agissent simultanément lorsqu'ils sont administrés par voie intramusculaire ou intraveineuse. La promazine alourdit moins le malade que la chlorpromazine. Les résultats des épreuves de laboratoire ont déjà été rapportés antérieurement (*C. M. A. J.* 76: 442, 1957). Ces deux produits se ressemblent au point que l'un peut être substitué à l'autre sans interruption du traitement. La promazine serait le médicament par excellence dans le traitement des petits mentaux au dispensaire ou au cabinet de consultation.

VIROLOGICAL INVESTIGATIONS IN ADENOVIRUS INFECTIONS OF THE CONJUNCTIVA, TORONTO, 1955-56*

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RESEARCH in the last five years has led to the discovery of a new group of viruses which cause infections of the respiratory tract and the conjunctival sac. Members of this group are now referred to as adenoviruses.[1] These agents were first demonstrated by Rowe *et al.*[2] in 1953 in spontaneously degenerating tissue cultures of human adenoids. At the present time, 14 distinct antigenic types have been recognized. These strains share a common complement fixing antigen, and produce characteristic cytopathogenic changes in tissue cultures of monkey kidney, human epithelium, and HeLa cells.[3, 4] In 1954, Hilleman and Werner[5] isolated other members of the group from cases of acute respiratory disease (ARD) in military recruits. Bell and co-workers[6] in 1954 studied a widespread epidemic of a disease which they termed pharyngoconjunctival fever, and from which adenovirus Type 3 was readily isolated. This epidemic closely resembled one described by Cockburn[7] which occurred in Greeley, Colorado, in 1951.

In 1955 Jawetz and co-workers in San Francisco isolated a strain of virus from a case of epidemic keratoconjunctivitis (EKC). This virus has been found to belong to the adenovirus group, and has been designated Type 8.[4, 8]

Epidemic and sporadic cases of infection attributed to adenoviruses have also been reported since 1955 from England by Zaiman, Balducci and Tyrrell,[9] and from Sweden by Kjellén.[10]

In Canada, adenovirus infections were probably first recognized as early as 1951, when an outbreak of epidemic keratoconjunctivitis at the Ford Motor Plant in Windsor, Ontario, was studied in the laboratory.[11] Attempts to isolate a virus at this time were not successful, but convalescent sera from patients in this epidemic were later found to contain neutralizing antibody to Type 8 adenovirus.[8]

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No further cases of conjunctivitis of probable viral etiology were reported in Canada until the winter of 1954-55, when more than 20 adults with follicular conjunctivitis were studied by one of us (H.L.O.).[12] About half of these patients developed corneal opacities. Serum taken from one of these patients showed neutralizing antibodies to adenovirus Type 8, but no virus was isolated from this patient. From four other patients with corneal opacities, Type 3 adenovirus was isolated, and neutralizing antibodies to this strain were demonstrated in convalescent sera.

During 1955-56, numerous cases of viral conjunctivitis were seen in Toronto in both children and adults. Laboratory investigations were carried out on cases in the epidemic of pharyngoconjunctival fever described by Ormsby and Aitchison,[13] and on sporadic cases of conjunctivitis seen in Toronto eye clinics and at The Hospital for Sick Children, Toronto. Four different types of adenovirus were isolated.[14] This paper reports the laboratory findings in 56 of such cases.

MATERIALS AND METHODS

Tissue Cultures

HeLa cells were grown in 20% human serum in yeast extract medium.[15] Before inoculation, tube cultures were washed three times with Hanks' balanced salt solution; maintenance medium, consisting of 10% rabbit serum in synthetic Medium No. 199, was then added.

Monkey kidney cells in suspension were obtained from the Connaught Medical Research Laboratories, University of Toronto. Tube cultures were propagated in a mixture of Hanks' balanced salt solution, 0.5% lactalbumen hydrolysate, and 2% horse serum. When ready for use, cultures were maintained in Earle's balanced salt solution, 0.5% lactalbumen hydrolysate, and 0.1% yeast extract.

Amnion cell cultures used early in the study were prepared as described by Beale, Doane and Ormsby.[14] Later the method was modified as follows.[16, 17] Placentas were collected into a sterile two-litre beaker containing about 300 ml. of Hanks' balanced salt solution, and were kept at room temperature. In the laboratory, the placenta was suspended by the umbilical cord; the amnion was carefully dissected from the chorion, and was washed several times in balanced salt solution containing antibiotics to remove blood and debris. The washed amniotic membrane was then transferred to a 250 ml. centrifuge bottle containing 100 ml. of 0.25% trypsin at pH 7.4-7.6. This solution was discarded after one hour, and was replaced with 100 ml. of fresh trypsin. After four to five hours at room temperature, most of the cells had been released into the solution, and the cell suspension was then filtered through one layer of gauze into a 250-ml. centrifuge bottle. The undigested portion of the membrane was rinsed well in two or three changes of balanced salt solution, a step which greatly increased the cell yield. The rinses were pooled and filtered into the centrifuge bottle, which was then centrifuged at 1000 r.p.m. for 20 minutes. The supernatant trypsin solution was discarded, and the packed cells were resuspended in a graduated centrifuge tube to a volume of 10 ml. The suspension was well mixed by using a syringe with a No. 18 needle.

A cell count was made by adding 0.1 ml. of cell suspension to 0.5 ml. of 0.1% crystal violet in 0.1 M. citric acid. Cells were then diluted to a final concentration of 3.5×10^5 per ml. in propagating medium, which consisted of 20% human serum in 0.5% lactalbumen hydrolysate and Hanks' balanced salt solution, at a pH of 7.4. A final volume of 60 ml. was added to 1-litre Pyrex "Blake" bottles, and 1 ml. to tubes. All cultures were kept at 37° C., and were given a complete change of medium every three to four days.

After 10-14 days, tube cultures were ready for inoculation; the following nutrient mixture was used: 1 part Medium No. 199 (Earle's base), and 1 part Earle's balanced salt solution with 0.5% lactalbumin hydrolysate and 0.1% yeast extract, with 2% horse serum. Bottle cultures were either trypsinized for "second generation" cultures or were kept at 31° C. until ready for use.

Bottle cultures ready for trypsinizing were washed with 40 ml. of balanced salt solution to remove dead cells. To each bottle was added 40 ml. of 0.25% trypsin; the bottle was then incubated for 15 minutes, or until the cell sheet had been dislodged from the glass surface. The cell suspension was centrifuged at 1000 r.p.m. for five minutes. The supernatant was discarded, and the cells were resuspended in 10 ml. of propagating medium, using 20% horse serum instead of human serum. The final dilution of cells, prepared in this medium at pH 7.4-7.6, was $1.0\text{-}1.5 \times 10^5$ per ml. Tube cultures were seeded with 1 ml. of this suspension, and were generally ready for use within four to five days. Inoculated cultures were grown in maintenance medium described above. This medium was changed every 10-14 days.

Collection of Specimens

Virus investigations were carried out on patients with conjunctivitis, seen by us during 1955-56. The clinical findings of these cases were suggestive of adenovirus infection. All patients studied were from one of the following groups: (1) An epidemic of pharyngoconjunctival fever in which contact in a Toronto swimming pool was incriminated.[13] (2) Patients referred to one of us (H.L.O.) from ophthalmologists in Toronto eye clinics. (3) Patients

admitted to The Hospital for Sick Children, Toronto.

Eye washings and throat swabs were collected in 1 ml. of Medium No. 199 and were stored at –20° C. On the basis of the recommendation of Bell *et al.*,[4] only those specimens taken within 10 days of the onset of illness were tested for the presence of virus.

Virus Isolations

Specimens were inoculated into HeLa cell or human amnion cultures in a volume of 0.1 ml. per 0.9 ml. of maintenance medium. Cultures were examined daily. When cytopathogenic changes suggestive of virus infection were detected, fluids were passed to a second set of cultures for confirmation. If typical cytopathogenic changes were not observed within two weeks, or before the occurrence of tissue degeneration from natural causes, fluid and cells were harvested and passed to fresh cultures.

The extent of specific virus-induced change in the cells constituting the epithelial sheet was graded according to the approximate number of cells showing the characteristic degeneration: changes involving less than 25% of the cell sheet +; changes involving 25-50% of the cell sheet ++; changes involving 50-75% of the cell sheet +++; changes involving 75-100% of the cell sheet ++++.

Preparation of Prototype Virus Pools

Prototype adenovirus strains 1-11 were kindly provided by Dr. R. J. Huebner. Individual pools of virus were prepared by the inoculation of HeLa cell tube cultures with a dilution of virus calculated to bring about complete destruction (++++) of the cells within four to five days. Infected cultures and fluids were harvested and pooled, and refrozen three to four times to break up the cells. Pools were then clarified by centrifugation, and dispensed into small screw-capped vials for storage at –20° C.

Preparation of Antisera

Immune sera against the adenovirus prototypes were prepared in rabbits by means of five twice-weekly intravenous injections of 1.5 ml. of tissue culture fluid.[17] Blood was collected by cardiac puncture one to two weeks after the last inoculation.

Typing of Virus Isolates

Virus isolates were first tested against mixtures of two or three adenovirus antisera, prepared in rabbits. When a serum mixture completely neutralized the virus under test, as evidenced by the absence of typical cytopathogenic changes, the virus was typed against the individual sera comprising that mixture. Final readings were made 48 hours after the virus control cultures showed cytopathogenic changes graded as +++. A virus was assigned to a particular adenovirus type on the basis of complete neutralization by antiserum to that type.

Antibody Tests on Patient's Sera

The level of neutralizing antibody in human sera was determined by "Procedure 2" suggested by Rowe *et al.*[17] Tests were carried out in monkey kidney cultures using a concentration of prototype virus calculated to produce +++ cytopathogenic changes on the second to third day. Final readings were made 24 hours later. The titre of the serum was taken as the highest dilution producing complete neutralization of virus.

The techniques employed in the determination of complement fixing antibody were essentially those described by Bengtson.[18]

The antigen used in complement fixation tests was prepared from HeLa cell cultures infected with Type 3 virus by heating at 56° C. for 30 minutes. In the test, two units of antigen and two exact units of complement were used.

The hæmolytic system was composed of equal quantities of a suspension of 2% sheep cells and hæmolysin diluted so that two units were contained in each 0.2 ml. Patients' sera were inactivated at 56° C. for 30 minutes. Serum, antigen and complement were added in 0.2-ml. amounts to serological test tubes, and were then incubated overnight at 4° C.

Quantities of 0.4 ml. of sensitized sheep cells were added to the tubes after they had stood at room temperature for 30 minutes; tubes were placed in a 37° C. water bath for 30 minutes, and readings were taken after they had stood at room temperature for 30 minutes. The CF titre of the serum was determined on the basis of the highest dilution which allowed greater than 50% fixation.

RESULTS

Isolation and Typing of Viruses

Eye washings from 56 patients were examined by the inoculation of HeLa cell or human amnion cultures. A total of 33 patients yielded adenoviruses in eye washings. The results are given in detail in Table I. The three strains isolated from patients in the swimming pool epidemic were all adenovirus Type 7. Types 3, 7 and 9 were isolated from the eye clinic patients, and Types 2, 3 and 7 from the hospital children. In the whole group, there was one isolation of Type 2, 15 of Type 3, 14 of Type 7, and three of Type 9.

TABLE I.—ISOLATION AND TYPING OF ADENOVIRUS STRAINS FROM PATIENTS WITH CONJUNCTIVITIS, TORONTO, 1955-56

Source	*Number of patients tested*	*Number of patients yielding adenovirus*	*Number of strains of following adenovirus types isolated*			
			2	*3*	*7*	*9*
Swimming pool epidemic	6	3			3	
Eye clinics	39	22		12	7	3
Hospital for Sick Children	11	8	1	3	4	
Total	56	33	1	15	14	3

The superiority of human amnion cells to HeLa cells for the study of adenoviruses has been alleged.[14] More recently, we have found that while amnion cell cultures are readily maintained over long periods of time, and exhibit easily recognized cytopathogenic changes following adenovirus infection, they are not as sensitive as HeLa cells for all the adenovirus types.

Serology

Acute and convalescent phase sera from 15 of the 33 patients from whom adenoviruses were isolated were tested for both neutralizing and complement fixing antibodies to this virus. The results are given in Table II. A fourfold or greater rise in both types of antibody was demonstrated in 12 cases. One patient showed a rise in neutralizing antibody only, one showed a rise in CF antibody only, and one patient showed no rise in either type of antibody.

In addition, paired sera from seven patients from whom no virus was isolated were tested for complement fixing antibody. Five of these patients showed no antibody in either acute or convalescent samples; a distinct rise in CF antibody, however, was demonstrated in the sera of two patients, suggesting that these were in fact infected with adenoviruses.

The group specific CF antibody which can be demonstrated in serum following adenovirus infection appears to be transient in nature. Van Horne *et al.*[19] have recently reported the results of a study of a family epidemic of pharyngo-conjunctival fever. Significant rises in titre of both type-specific neutralizing antibody and group-specific CF antibody were demonstrated during the acute phase of illness, but when the serological studies were repeated seven months later, no CF antibody could be demonstrated, although the neutralization titres remained elevated. In view of these findings, the results of our CF tests suggest that infections

TABLE II.—SEROLOGICAL RESULTS ON PAIRED SERA FROM PATIENTS FROM WHOM ADENOVIRUSES WERE ISOLATED

Patient's reference number	*Age (years)*	*Adenovirus type isolated from eye washings*	*Days after onset serum collected*		*Neutralizing antibody titre†*		*CF antibody titre‡*	
			*S1**	*S2**	*S1*	*S2*	*S1*	*S2*
2	21	3	4	11	<4	32	<4	32
23	53	3	3	11	<4	8	<4	32
27	25	3	4	40	<4	32	<4	32
43	35	3	3	13	<4	32	<4	16
50	24	3	5	54	<4	16	<4	32
57	49	3	8	29	<4	32	<4	16
62	23	3	3	22	<4	16	<4	32
64	25	3	4	14	<4	16	<4	< 4
67	30	3	4	19	<4	64	<4	64
7	24	7	6	27	<4	32	<4	16
9	25	7	5	33	<4	64	<4	64
21	8	7	3	7	<4	16	<4	32
38	1	7	6	10	<4	< 4	<4	< 4
46	29	7	4	26	<4	< 4	<4	32
20	13	9	5	29	<4	8	<4	32

*S1 = acute phase serum. S2 = convalescent phase serum.
†Against prototype virus. ‡Against Type 3 antigen.

by adenoviruses of any type only rarely occurred in the Toronto area during the period immediately preceding the study.

SUMMARY

1. Virological investigations were performed on epidemic and sporadic cases of conjunctivitis in the Toronto area, 1955 and 1956. From 56 such cases, 33 adenovirus strains were isolated from eye washings.

2. Adenovirus Type 7 was implicated in an epidemic of pharyngoconjunctival fever among children attending a Toronto swimming pool.

3. Adenovirus Types 2, 3, 7 and 9 were isolated from sporadic cases of conjunctivitis.

4. Serological tests were carried out on paired sera from 15 of the 33 patients from whom adenoviruses were isolated. A significant rise in both neutralizing and complement fixing antibody levels was demonstrated in 12 of these patients. One patient showed a rise in neutralizing antibody only, one showed a rise in complement fixing antibody only, and one patient showed no rise in either type of antibody.

We would like to acknowledge the co-operation of the numerous physicians in Toronto who afforded access to their patients.

REFERENCES

1. ENDERS, J. F. *et al.*: *Science*, **124**: 119, 1956.
2. ROWE, W. P. *et al.*: *Proc. Soc. Exper. Biol. & Med.*, **84**: 570, 1953.
3. ROWE, W. P. *et al.*: *Am. J. Hyg.*, **61**: 197, 1955.
4. ROWE, W. P., HARTLEY, J. W. AND HUEBNER, R. J.: *Proc. Soc. Exper. Biol. & Med.*, **91**: 260, 1956.
5. HILLEMAN, M. R. AND WERNER, J. H.: *Ibid.*, **85**: 183, 1954.
6. BELL, J. A. *et al.*: *J. A. M. A.*, **157**: 1083, 1955.
7. COCKBURN, T. A.: *Am. J. Ophth.*, **36**: 1534, 1953.
8. JAWETZ, E. *et al.*: *Science*, **122**: 1190, 1955.
9. ZAIMAN, E., BALDUCCI, D. AND TYRRELL, D. A. J.: *Lancet*, **2**: 595, 1955.
10. KJELLÉN, L.: *Arch. ges. Virusforsch.*, **6**: 45, 1955.
11. MCGAVIN, M. F., BOLEY, J. P. AND ORMSBY, H. L.: *Canad. M. A. J.*, **69**: 137, 1953.
12. ORMSBY, H. L., FOWLE, A. AND COCKERAM, A.: *Ibid.*, **73**: 710, 1955.
13. ORMSBY, H. L. AND AITCHISON, W. S.: *Ibid.*, **73**: 864, 1955.
14. BEALE, A. J., DOANE, F. AND ORMSBY, H. L.: *Am. J. Ophth.*, **43**: (No. 4, part 2) 26, 1957.
15. ROBERTSON, H. E., BRUNNER, K. T. AND SYVERTON, J. T.: *Proc. Soc. Exper. Biol. & Med.*, **88**: 119, 1955.
16. ZITCER, E. M.: Personal communication.
17. WEINSTEIN, H. J. *et al.*: *Proc. Soc. Exper. Biol. & Med.*, **92**: 535, 1956.
18. BENGTSON, I. A.: *Pub. Health Rep.*, **59**: 402, 1944.
19. VAN HORNE, R. G. *et al.*: *A.M.A. Arch. Int. Med.*, **99**: 70, 1957.

RÉSUMÉ

Des recherches virologiques furent pratiquées dans la région de Toronto en 1955 et 1956 chez des sujets atteints de conjonctivite de forme épidémique ou sporadique. Trente-trois types d'adénovirus furent isolés des sécrétions oculaires de 56 malades. Un adéno-virus de type 7 fut incriminé dans une épidémie de fièvre pharyngo-conjonctivale chez des enfants s'étant baignés dans une piscine de Toronto. On isola les types 2, 3, 7 et 9 chez des cas sporadiques de conjonctivite. Les épreuves sérologiques pratiquées chez 15 malades montrèrent une élévation sensible du taux des anticorps neutralisateurs et de ceux des fixateurs du complément chez 12 d'entre eux. On observa l'élévation d'un seul de ces taux chez deux malades, et un troisième n'en montra aucune.

SOME OBSERVATIONS ON GLOMERULAR VASCULAR ARCHITECTURE*

MATTHEW J. G. LYNCH, M.B., M.R.C.P.(Lond.), F.C.A.P.,† *Sudbury, Ont.*

BOWMAN'S[1] ORIGINAL observation that all blood must pass through the glomeruli to reach the tubules has not been seriously challenged even to this day. In 1857 Isaacs[2] described branches arising from the afferent arterioles and joining the capillary intertubular plexus. This Isaacs-Ludwig branch, or, as it is more commonly known, "Ludwig's arteriole", has been recognized by many workers, including Loomis,[3] though MacCallum[4] ascribes such branches to "non-glomerular transformation by glomerular pathological circulatory readjustment", and asserted that normal renal circulation was glomerular. Spanner[5] gave a convincing demonstration of the extent of arteriovenous anastomoses in the cortex, and Trueta and his coworkers[6] believed that all aglomerular vessels of the Isaacs-Ludwig type are ones from which the glomeruli have atrophied because of shunt formation by over-development of one capillary loop of the glomerular tuft. Thus, though Trueta *et al.* showed very beautifully the extent and importance of by-pass circulation in the kidney, they nevertheless were adamant that all renal circulation was primarily glomerular, and that even the extensive cortical by-pass mechanism operated through the 15% of glomeruli situated in the juxtamedullary regions. Personal observations suggested that certain micro-anatomical features of the glomerulovascular unit had been overlooked or had been inadequately described, and it was decided to investigate these using

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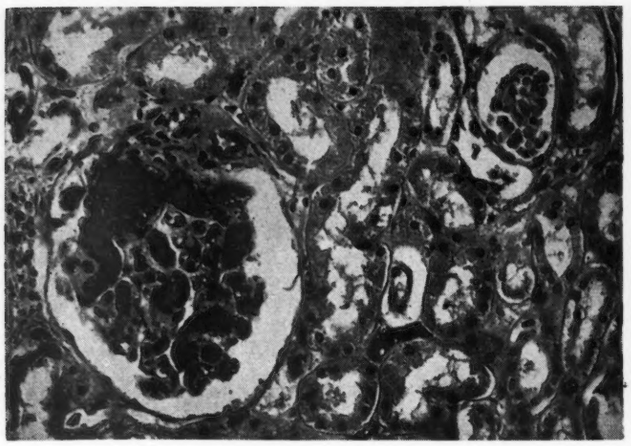

Fig. 1

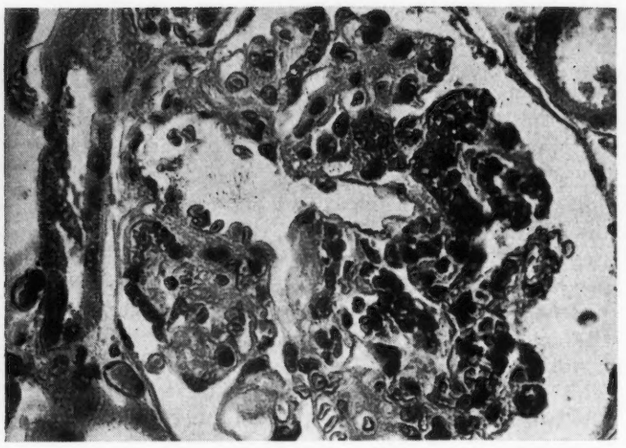

Fig. 2

Fig. 1.—Glomerulus showing dilated and congested afferent arteriolar hilar distribution pool. Above it is the juxtaglomerular apparatus, and in the right corner of this the efferent arteriole is seen in section. × 300. **Fig. 2.**—Hilar distribution pool, dilated and almost empty. × 630.*

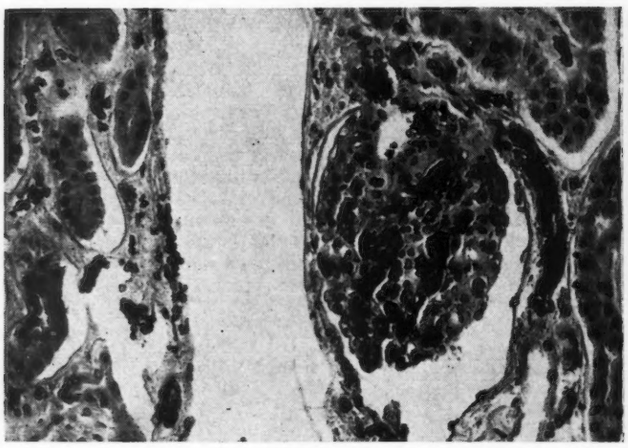

Fig. 3

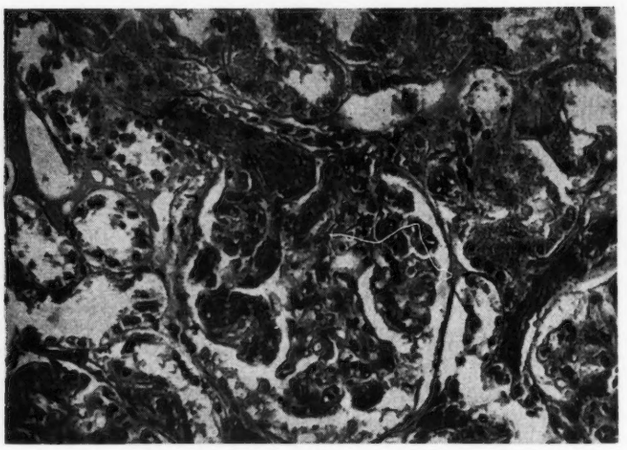

Fig. 4

Fig. 3.—Glomerulus showing afferent arteriole and its pool (top left). The efferent arteriole hugs the capsule on the right. × 300. **Fig. 4.**—Adult glomerulus showing polarity of spongework cells of juxtaglomerular apparatus between afferent arteriole (top left) and efferent. × 300.

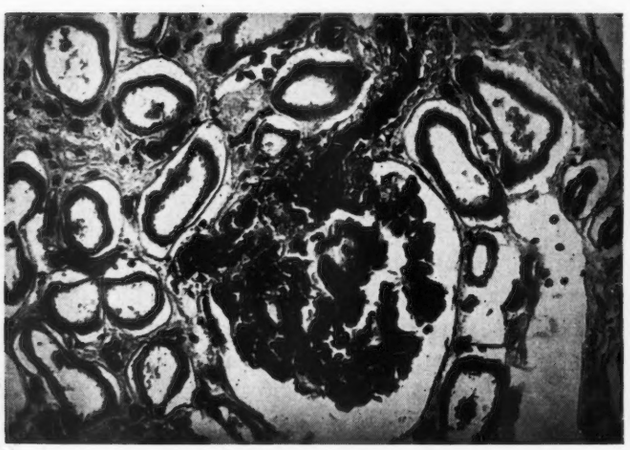

Fig. 5

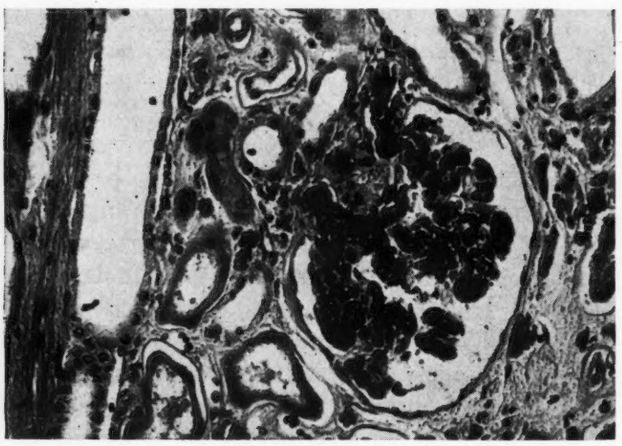

Fig. 6

Fig. 5.—Outer cortical glomerulus: Goormaghtigh shunt between afferent (top right) and efferent (left side of top) arterioles. × 300. **Fig. 6.**—There is a short connecting channel between the afferent (top right) and efferent (left) arteriolar pools. × 300.

*All photomicrographs are from non-diseased kidneys.

methods that would not be open to criticism on the grounds of artefaction or distortion due to injection masses, pressures, etc.[5, 6]

Materials and methods.—Serial sections of routine autopsy material which had been fixed in buffered neutral formalin were cut at 5μ thickness. All blocks included the whole thickness of the cortex and at least half of the medulla, and measured approximately 1½ x 2¼ cm. in area. The sections were mounted in serial order, three to each slide. Hæmatoxylin and eosin staining was used throughout. The middle section on each slide was examined in detail. When a feature of interest was noted, it was then scrutinized in the sections on either side, and followed proximally or distally, or in both directions. In this way some 200 glomeruli were followed completely, and the vascular poles of many times this number were studied. The cases investigated are detailed in the accompanying table. With the exception of the obvious nephropathies, the cases were chosen on the basis of absence of renal disease and the presence of passive renal congestion, since the natural injection mass of erythrocytes is undoubtedly the best means of demonstrating vascular channels.

TABLE I.—CASES STUDIED

Case No.	*Dept. No.*	*Sex*	*Age*	*Pathological findings*	*No. of sections in series*
1	A 71/55	F	66	Ca. breast; 2° liver; obstructive jaundice; chronic pancreatitis	45 and 57
2	A124/56	M	39	Kimmelstiel-Wilson nephropathy; necrotizing pancreatitis	18
3	A163/56	F	61	Diabetes; Kimmelstiel-Wilson glomerulonephropathy	18
4	A203/56	M	56	Acute coronary artery thrombosis	75 and 52
5	A216/56	M	41	Acute toxic (alcoholic) thrombotic glomerulonephropathy	45
6	A217/56	M	19	Meningeal hæmorrhage; Marfan's syndrome	66
7	A 8/57	F	2½	Staphylococcal pneumonia; morbilli	45
8	A 10/57	F	2	Lung metastases; sympathico-blastoma of sciatic nerve	15
9	A 12/57	M	68	Cardiac tamponade; rupture of atheromatous aorta	93
10	A 15/57	M	44	Acute coronary artery thrombosis	32
11	A 16/57	F	43	Cerebral hæmorrhage; benign hypertension	31
12	A 22/57	M	5 hrs.	Hyaline membrane disease of lungs; prematurity (28 weeks)	18
13	A 24/57	M	51	Uræmia due to electrical burns sustained 8 days before death	18

FINDINGS

1. *Hilar distribution pool.*—In all cases the afferent arteriole, on entering the glomerulus, appears to form or expand into a large pool having two to six (commonly three) branches (Figs. 1, 2 and 3). The glomerulus, as it were, sits on this pool much as a lamp shade sits on its base. Study of this pool from the same and different cases clearly reveals that it is a dynamic physiological structure, capable of great dilation, alteration of shape, and of contraction to the point of occlusion. It appears also that its contraction or occlusion may be complete or incomplete, symmetrical or asymmetrical. Its branches often interdigitate with those which go to form the smaller efferent pool, and occasionally one sees short channels connecting the two pools as they lie close together in the "socket" of the glomerulus (Fig. 6).

2. *Efferent pool and efferent arteriole.*—The efferent capillaries of the glomerular tuft appear to run to two or three main branches near the centre of the glomerulus and fuse to form the efferent pool. This latter is much smaller than the afferent arteriolar pool, being rarely more than half its size. Furthermore, it is generally more elongated and narrow than the afferent pool, and is occasionally seen to reach to the centre of the glomerulus. From this smaller pool the efferent arteriole arises. Immediately on emerging from the capsule, it turns or bends sharply, almost always in a direction away from the line of approach of the afferent arteriole, and follows the capsule closely for a considerable distance—indeed, more often than not to the opposite pole of the glomerulus. In this course it is commonly noticed to give off branches which also follow the capsule. No exception to this juxtacapsular course of the efferent arteriole was found in the many hundreds of instances examined (Figs. 3, 7 and 8).

3. *Shunts and by-passes.—The juxtaglomerular apparatus*: Frequently the interlobular (intralobular) and afferent arterioles were observed to give off small branches. When these capillary-like twigs were followed serially, they were seen to merge with the intertubular capillary plexus. In addition, in a number of instances the afferent arteriole was seen, quite close to the vascular pole of the glomerulus, to give off a tiny twig which ran to the capsule and merged with the pericapsular capillary plexus.

The juxtaglomerular apparatus was easily visualized in all cases examined, with the exception of the premature infant (Case 12). Only in one outer cortical glomerulus could no vestige of this structure be found. Generally speaking, this apparatus was most prominent in the juxtamedullary glomeruli, but there were frequent exceptions to this, and it was exceedingly well developed in all parts of the cortex of a case of nodular and diffuse Kimmelstiel-Wilson glomerulonephropathy (Case 3). Not infrequently the apparatus extended deeply into the glomerular hilus to continue into the walls of the hilar distribution pool. Indeed, in some instances almost the whole apparatus was invaginated into the hilus.

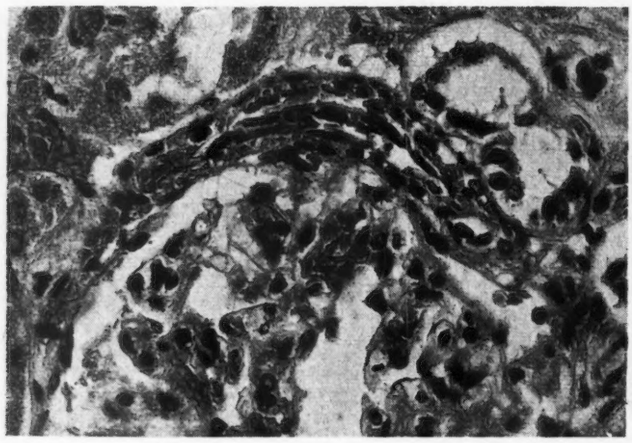

Fig. 7

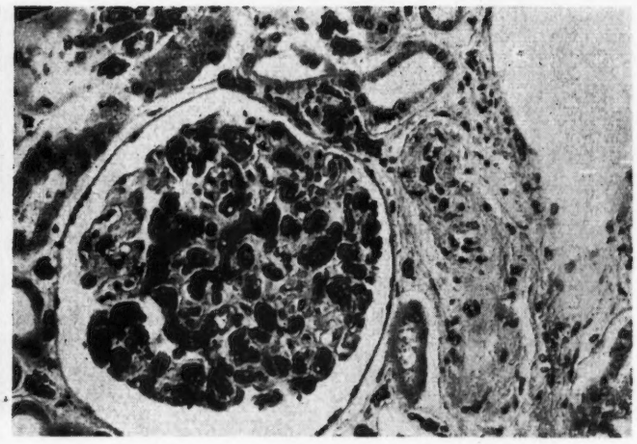

Fig. 8

Fig. 7.—Double channel shunt in Goormaghtigh apparatus. See text. × 630. Fig. 8.—Efferent arteriolar "sleeve shunt". See text. × 300.

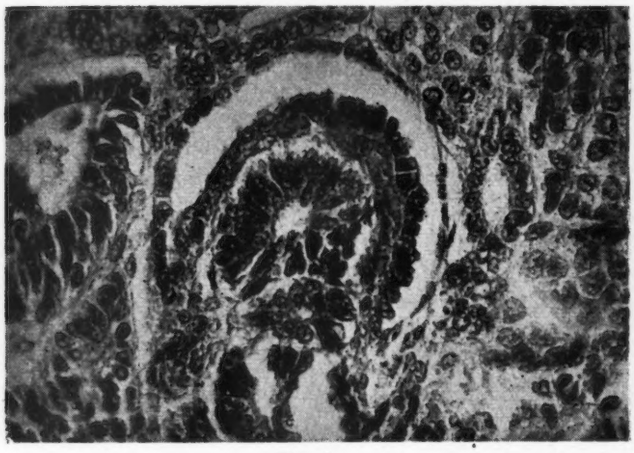

Fig. 9

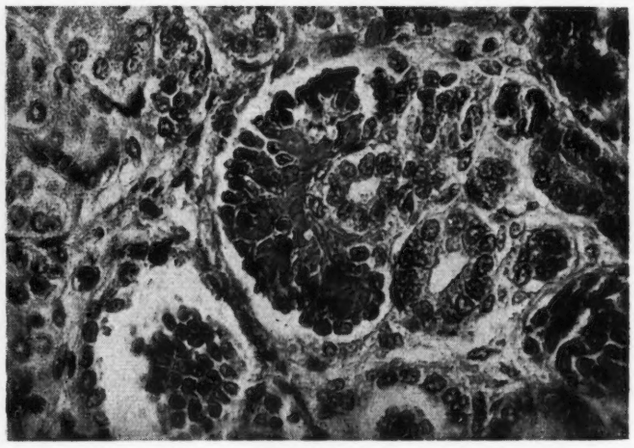

Fig. 10

Fig. 9.—Developing glomerulus: a single vessel separates the visceral layer of the capsule from the cellular macula densa of the tubule. × 630. Fig. 10.—Developing glomerulus: further stage: the vessel has budded, and cells are growing down between the buds from the visceral layer of the capsule. These cells will form "podocytes"(7) of adult. × 630.

It was obvious early in the investigation that the polarity or direction of lie of the cells and nuclei of the juxtaglomerular apparatus was of great significance. The greater number of its cells and nuclei were always oriented in the line joining the afferent and efferent arterioles (Figs. 1, 4 and 7). Indeed, one was invariably able to forecast the site of emergence of the efferent arteriole by observing the direction of these cells. Next, and of paramount importance, it was noticed in many instances that the arrangement of these juxtaglomerular cells suggested a closed or, sometimes, partly open vascular channel (Fig. 4) connecting the afferent and efferent arterioles. In many examples where this channel appeared to be tightly closed isolated erythrocytes were noticed sandwiched between its cells. Following these observations, intensive search of serial sections of suitably congested glomeruli revealed many instances of patent and obvious shunts through the juxtaglomerular (often partly intrahilar!) apparatus (Fig. 5). However, for each unequivocal shunt which was found several less obvious by-passes were detected by detailed and painstaking scrutiny of serial sections. In these cases acute bends and kinks in the channels rendered the shunt routes extremely difficult of detection. Frequently additional by-passes between the afferent and efferent channels were found deep in the hilus, and appeared to connect the afferent hilar distribution pool with the smaller efferent pool (Fig. 6). Occasionally atrophic juxtamedullary glomeruli were seen in which the juxtaglomerular by-pass was the only open channel. In some instances a clear double channel was noted (Fig. 7). On following these serially it was found that the outer (shunt) channel finally fused with the inner channel, which constituted the efferent arteriole in its characteristic juxtacapsular course. Though the majority of patent afferent-efferent shunts were found in the juxtamedullary region, a large number of open by-passes were also discovered in the outer cortex, and these generally displayed much less degenerative change (Fig. 5) than the juxtamedullary ones did.

Peculiar "sleeve shunt".—This was a rare feature, being observed in only three instances. However, it is described because of its peculiar arrangement and extent. In the one here partly illustrated (Fig. 8) serial sections showed that the efferent arteriole branched on emerging from the hilus. One of its branches then divided in Y fashion, and its limbs gradually encircled the main branch of the efferent or parent vessel, finally forming a continuous sleeve around this for a distance of at least 70 μ (14 sections). At four points there was direct communication between the central or main branch of the efferent arteriole and its surrounding sleeve (Fig. 8). The "sleeve" branch followed the parent efferent's main or central branch for 105 μ, giving off numerous intertubular twigs on its way. The main, central branch of the efferent arteriole hugged the capsule of the glomerulus for a distance of 155 μ, and then broke up into intertubular capillaries. The three examples of this most unusual sleeve arrangement of the efferent arteriole were all found in the outer cortex.

4. *Glomerular development.*—Though only one case was studied serially, the observations here recorded were sufficiently clear-cut and decisive, and have been supported by examination of routine slides from autopsy material of premature and full-term infants. The end of the tubule which is destined to form Bowman's capsule assumes a crescent shape, and, as it does so, the contiguous vessel is pressed on by the convex side. This appears to account for the juxtacapsular course of the efferent arteriole. The proximal part of the same vessel is pushed into the concave part of the crescent by a loop of the distal convoluted tubule. At this stage the whole glomerular bud measures 35-75 μ (average 50 μ) in greatest diameter, and it contains only one blood vessel, which is present (in a somewhat flattened-out state) immediately beneath the visceral layer of Bowman's membrane (Fig. 9). In the next stage (Fig. 10), the single vessel has developed many peripheral and side buds. Growth of these buds, as it were, pushes the main vessel back towards the hilus. At the same time there is very active proliferation of the cells of the visceral layer of Bowman's epithelium, and these cells grow downwards between the vascular buds, thus constituting the first stage in lobulation of the glomerulus. One frequently gets the impression that many cells are split off from the actively proliferating juxtahilar side of the invaginated loop of the distal convoluted tubule, and that these cells accumulate in the concavity of the invaginated vessel. However, it is difficult to decide whether this is a constant feature or what its significance may be. It appears, however, that little if any interstitial tissue enters into the glomerular hilus between the tube and the glomerular vessel during development, and none seems to intervene between the vessel and the visceral layer of Bowman's capsule. The present investigation has not revealed how the final complicated arrangement of afferent and efferent loops in the tuft is developed. Study of consecutive serial sections from adult cases suggests that the afferent limbs of the tuft capillaries run a peripheral course in the glomerulus and that they frequently form a shallow half spiral before becoming continuous with the efferent limbs, which appear to run in the centres or axes of the tuft lobules.

DISCUSSION

It was not possible to find any reference to or description of the dilatation or pool of the afferent arteriole in available English literature. This feature was so striking that it appeared inconceivable that it should have escaped the attention of previous workers, and it was not surprising to learn from the excellent review of Elias[7] that Borst[8] had described this aspect of the afferent arteriole. However, study of the latter author's paper reveals only a passing mention of this structure: "It is seen that the lumen of the afferent arteriole, as it enters the glomerulus, forms a cavity which is sometimes round but mostly irregular." It appears to the present worker that the structure and function of this pool deserves far greater study. McGregor[9] observed that the vas afferens and its supporting framework passes well into the centre of the glomerulus before it breaks up into capillaries, but, as in the case of most observers, she failed to describe the afferent arteriolar pool. Smith[10] remarked ". . . there is as yet no evidence that the capillary tuft in the mammalian glomerulus has any intrinsic device for the regulation of the circulation. Glomerular activity is apparently determined entirely by the activity of the afferent and efferent arterioles." The classical studies of Richards and Schmidt[11] have shown that in cold-blooded animals individual glomeruli and even their capillary tufts open and close intermittently. All pathologists must be familiar with the commonly seen picture of one or two lobules of a glomerular tuft appearing markedly congested and filled with red blood cells, while others in the same glomerulus are completely empty and ischæmic. In the present investigation the muscular nature of the wall of the afferent arteriolar pool has been obvious in most instances (Figs. 3, 4, 5 and 6). Fig. 2 strongly suggests that selective contraction of parts of the wall of this pool would allow some lobules of the tuft to fill with blood, while others would remain empty. It is not inconceivable that this structure, for which the name "hilar distribution pool" is here advanced, may, by acting synergistically with the efferent arteriole, control the filtration pressure within the capillary

loops so that this may have a measure of independence of the systemic arterial pressure. Some support for such a concept is found in Zimmermann's[12] description of the "drop-like" protuberance of the endothelial cell nuclei of both afferent and efferent arterioles near the glomerulus. Indeed, Zimmermann speculated on the possible function of such nuclear arrangement in preventing back-flow. A further function of the hilar distribution pool will be evident in that, by shutting off blood flow through the tuft, it may allow shunting of the stream from afferent to efferent vessels via the short narrow channels which connect afferent and efferent pools (Fig. 6). Such short, narrow, anastomotic channels between afferent and efferent sides of the glomerular circulation have been described by Borst and by Zimmermann,[12] to mention but a few authors, but their existence has been denied by Vimtrup.[13]

The consistently juxtacapsular course of the efferent arteriole was a surprising finding in that no mention of this obvious structural relationship could be found. However, though it is never remarked upon, this course is evident in the photographs of neoprene casts of a number of authors, e.g. Trueta *et al.*[6] (their Figs. 34-36 and 44-46), Allen[14] (Figs. A, B and C, p. 33) and More and Duff.[15] Not much importance can be attached to this course of the efferent arteriole. It has a developmental importance as already indicated, and it may account for the true capsular lesions of Kimmelstiel-Wilson diabetic glomerulosclerosis. Examination of serial sections of two cases of this type in the current study supports this hypothesis, but has shown that the great majority of capsular lesions in this condition are actually tuft lesions that have fused with the capsule. The further practical importance of the juxtacapsular course of the efferent arteriole is twofold; viz. (a) this fact and the large size of the afferent hilar distribution pool offer a simple and ready means of identifying the two arterioles; (b) it appears that the capsule derives a large part of its blood supply from branches of the efferent arteriole. This last observation conflicts with that of Trueta and his co-workers,[6] who state that the glomeruli and their capsules are embedded in a venous capillary plexus. However, in this connection it is felt that Trueta's conclusions are not altogether correct. In his legend to Fig. 80 it is said that the capillaries filled from the efferent vessel do not surround the glomerulus or its convoluted tubule but are situated away from these. However, the legend admits that some glomerular capillaries were ruptured, and the present author believes that the high injection pressures used by Trueta and his group must have led to rupture and non-visualization of many fine branches and anastomoses.

In the work here reported aglomerular twigs have frequently been seen arising from afferent and interlobular arterioles and anastomosing with intertubular capillary plexuses. Furthermore, such twigs were seen at all ages, and in addition tiny capillaries were observed arising from the afferent arterioles near the glomerular hila and communicating with the pericapsular plexus. In many instances both types of branch have been seen springing from the same afferent arteriole.

In his original description of the juxtaglomerular apparatus Goormaghtigh[16] intimated that this neuro-myo-arterial structure might act as a shunt, though of late he implies that its main function is that of an endocrine gland secreting renin or other pressor substances.[17-19] Zimmermann[12] emphasized the asymmetrical shape and vascular sleeve nature of the juxtaglomerular apparatus or polar cushion (Polkissen), as he called it. The serial section studies here reported fully confirm this asymmetrical shape, and show it to be due to its extension from the afferent to the efferent arterioles. Close scrutiny reveals it to be a sponge-work, glomus-like body, and the main polarity of its cells appears to outline the chief potential channel through it. Contrary to the opinions of many,[10, 12, 16] it is believed that this mechanism is present in virtually all glomeruli, and from early childhood. Admittedly, in young children and in many adults it is small and easily overlooked unless serial sections are carefully studied, and even then its not uncommon partial intrahilar position may render it difficult to visualize. It appears also that its natural inactive state is a closed one, hence it is so difficult to suspect or demonstrate that it is a shunt. One of its main functions would seem to be that of regulating the state of activity of its own glomerulus, shunting the latter in and out of action. It is believed to assume special significance in the juxtamedullary glomeruli as a major shunt mechanism in by-passing the outer cortex, as Trueta and his collaborators have so convincingly shown. How-

ever, Trueta's conception of such a glomerular by-pass did not involve the juxtaglomerular apparatus, but assumed hypertrophy of one capillary loop of the glomerular tuft. The author's study suggests, however, that the intraglomerular capillary arrangement is far too complex to sustain this hypothesis. Again, many of Trueta's own illustrations (his Figs. 58, 59, 61 and 62) clearly show a short, thick shunt channel between the afferent and efferent arterioles in the outer regions of the hilus. The present study of serial sections has shown that many of these shunt channels in the juxtaglomerular apparatus are complex pathways, with bends and twists, and this would account for the kinks always observed by Trueta and his associates in the aglomerular shunt arterioles from which the glomerulus had atrophied from simple disuse. It is to be noted that MacCallum[4] described and illustrated such shunts, but he rigidly ascribed them to pathological changes in the glomeruli, though he failed to describe the nature or cause of this pathology; he was unable to determine the origin of the "anastomotic" vessel, which he depicted in the peripheral edge of the vascular pole, though he described it as being within the capsular space. Perhaps the greatest criticism that can be levelled against MacCallum's reasoning is that he failed to entertain the obvious consideration, viz. that a glomerulus which is continuously bypassed will atrophy through simple ischæmia, thus obviating the necessity to postulate some obscure "glomerular pathological circulatory readjustment".

It is not surprising that Trueta and MacCallum noticed similar degeneration in outer cortical glomeruli, for it appears that virtually all glomeruli possess this shunt mechanism, though it is the juxtamedullary ones which are most used in the massive cortical by-passing system. How often shunts are operative in the outer cortical glomeruli cannot be even guessed at from this morbid study, but it does appear likely that individual glomeruli are not continuously at work, and the present study may supply a structural basis for the discrepancies so often noted in dynamic renal function tests. The author does not wish to appear to decry Goormaghtigh's contention that the apparatus which bears his name may have in addition a hormone-secreting function. No opinions are held or offered on this possibility, and the author has no experience on which to base any. Nevertheless, it is felt that the prime purpose of the Goormaghtigh apparatus is that of providing an afferent-efferent shunt for by-passing the glomerulus, and in a massive manner in the case of the juxtamedullary glomeruli for short-circuiting the outer cortex. It will thus be apparent that the glomerulus has two possible by-passes, i.e. between the pools of its arterioles, and between these arterioles themselves. Either or both of these may be in action at one time, and either may be potentiated by synergistic action of the hilar distribution pool. That such short connections should exist between afferent and efferent arterioles is not surprising if the author's conclusions as to glomerular vascular development from one invaginated vessel are correct. Indeed, this mode of development appears more likely and plausible than the "advancing cluster of capillaries" or "vascular knot" of some authors.

Two cases (7 and 13) in the present study provided examples of severe cortical ischæmia. Detailed study of these showed that, while in the vast majority of glomeruli the afferent arteriole, its pool and the glomerular tuft were open and even moderately dilated and well filled with blood, in almost all instances the efferent arterioles were completely closed and empty. While one is aware of the possible error in drawing conclusions from such material, one is nevertheless inclined to think that perhaps spasm of the efferent arterioles may be the more important etiological factor in these cases—at any rate in perpetuating the cortical ischæmia after the initial reflex spasm of the interlobular and afferent arterioles has passed off. This would account for the frequent finding of glomerular congestion in such cases—a point that is well brought out by Trueta and his associates. In this connection it is worthy of recall that renal function studies led Smith[10] to believe that adrenaline acted on the efferent arterioles.

SUMMARY

The study is based on examination of serial sections from 13 autopsy cases ranging from a premature infant of 28 weeks' gestation to an adult of 68 years.

The widening of the afferent arteriole as it enters the hilus of the glomerulus is described, and reasons are put forward for calling it the "hilar distribution pool". It is shown that the efferent arteriole follows, without exception, a close juxtacapsular course for a considerable distance after emerging from the glomerulus.

Short-circuiting connections are described and illustrated between the afferent hilar distribution pool and the efferent arteriolar pool. The function of the juxtaglomerular Goormaghtigh apparatus as a shunt between the afferent and efferent arterioles is outlined. Embryological findings are discussed in support of the above findings.

Appreciation is recorded to Dr. A. L. Chute and to Dr. H. W. Bain of The Hospital for Sick Children, Toronto, for their encouragement and interest. Thanks are due to Mrs. I. B. Eley for the many sections prepared in the course of this study.

REFERENCES

1. BOWMAN, W.: *Phil. Tr. Roy. Soc. Lond.*, **132**: 57, 1842.
2. ISAACS, C. E.: *Tr. New York Acad. Med.*, **1**: 377, 1857.
3. LOOMIS, D.: *Arch. Path.*, **22**: 435, 1936.
4. MACCALLUM, D. B.: *Am. J. Anat.*, **65**: 69, 1939.
5. SPANNER, R.: *Anat. Anz*, **85**: (Erganzungsheft (*Verh. d. Anat. ges.*) **45**) 81, 1938.
6. TRUETA, J. *et al.*: Studies of the renal circulation, Charles C Thomas, Springfield, Ill., 1947.
7. ELIAS, H.: *Research in the Service of Medicine*, **46**: 3, 1956.
8. BORST, J. G. G.: *Ztschr. f. mikr.-anat. Forsch.*, **23**: 455, 1931.
9. MCGREGOR, L.: *Am. J. Path.*, **5**: 545, 1929.
10. SMITH, H. W.: *Harvey Lect. Ser.*, **35**: 166, 1939-1940.
11. RICHARDS, A. N. AND SCHMIDT, C. F.: *Am. J. Physiol.*, **71**: 178, 1924.
12. ZIMMERMANN, K. W.: *Ztschr. f. mikr.-anat. Forsch.*, **32**: 176, 1933.
13. VIMTRUP, B.: *Am. J. Anat.*, **41**: 123, 1928.
14. ALLEN, A. C.: The kidney: medical and surgical diseases, J. & A. Churchill, Ltd., London, 1952, p. 33.
15. MORE, R. H. AND DUFF, G. L.: *Am. J. Path.*, **27**: 95, 1951.
16. GOORMAGHTIGH, N.: *Arch. de biol.*, Paris, **43**: 575, 1932.
17. *Idem*: *Bruxelles-méd.*, **19**: 1541, 1939.
18. *Idem*: *Am. J. Path.*, **16**: 409, 1940.
19. *Idem*: *J. Path. & Bact.*, **57**: 392, 1945.

RÉSUMÉ

Les constatations dont fait part cet article sont basées sur l'examen de coupes histologiques en série provenant de 13 autopsies des sujets dont le plus jeune était un foétus de 28 semaines et le plus vieux, un adulte de 68 ans. On y décrit l'élargissement que subit l'artériole afférente comme elle pénètre le hile du glomérule. L'auteur donne ses raisons pour nommer cette structure le *tronc de distribution du hile*. L'artériole efférente suit toujours un trajet juxta-capsulaire sur une distance relativement considérable au sortir du glomérule. L'auteur fournit des descriptions et des illustrations de courts-circuits réunissant les troncs de distribution hilaire afférents et efférents. Il souligne la fonction de l'appareil juxta-glomérulaire de Goormagtigh comme shunt entre les artérioles afférentes et efférentes. Ces constatations sont appuyées par des données embryologiques.

CARDIAC INFARCTION IN VICTORIA, B.C.

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AN IMPORTANT POINT in regard to cardiac infarction is the frequency with which clear-cut diagnostic electrocardiographic tracings are obtained when infarction occurs. Clinically, of course, the diagnosis may range from the classical case to an extremely puzzling problem, and it is in the latter type that clear-cut E.C.G. changes are most helpful. But what of the puzzling clinical problem with the equally puzzling E.C.G.?

Interest was originally stimulated by clinical and pathological observation of one case of acute myocardial infarction, in which a 12 lead electrocardiogram failed to corroborate the event, but a review of available literature gave only a general answer to this question. This study was therefore undertaken to determine, as accurately as possible, what percentage of routine electrocardiograms taken in a non-teaching general hospital, in cases recorded clinically as myocardial infarction, are diagnostic of such an event.

METHODS AND MATERIALS

Two hundred and eighteen cases of acute myocardial infarction occurring through the years 1952-1953 have been collected from the medical records of Royal Jubilee Hospital, St. Joseph's Hospital, and Victoria Veterans' Hospital. This number represents, to the best of our knowledge, the entire hospital experience with acute myocardial infarction in Victoria, B.C., during those years.

Cases included in the study were carefully selected by the author, using any one of four criteria, listed in order of importance as follows:

1. A good clinical history suggesting the occurrence of cardiac infarction.

2. Autopsy evidence of recent myocardial infarction.

3. A pathognomonic E.C.G.

4. In the absence of a typical clinical history, a clear-cut pattern of infarction in the E.C.G. together with the usual white blood count and sedimentation rate changes was accepted.

It is emphasized that under point 1 cases were accepted if a clear-cut bedside diagnosis of infarction could be made, regardless of the support given by the E.C.G.

It was felt that such a selection procedure would throw more light on the clinical problem at hand than would a rigid selection of pathologically proven infarcts. The latter group includes, by its very nature, the majority of severe infacts; such a clinico-pathological correlation thereby produces a bias in favour of the electrocardiogram.

On the other hand, the selection of cases on a purely clinical basis encourages the inclusion in the series of some diagnostic errors.

In this study, however, a certain number of deaths which occurred among the individuals selected on the basis of point 1 afforded an opportunity for pathological confirmation of the above hypothesis. These cases will be discussed in detail below.

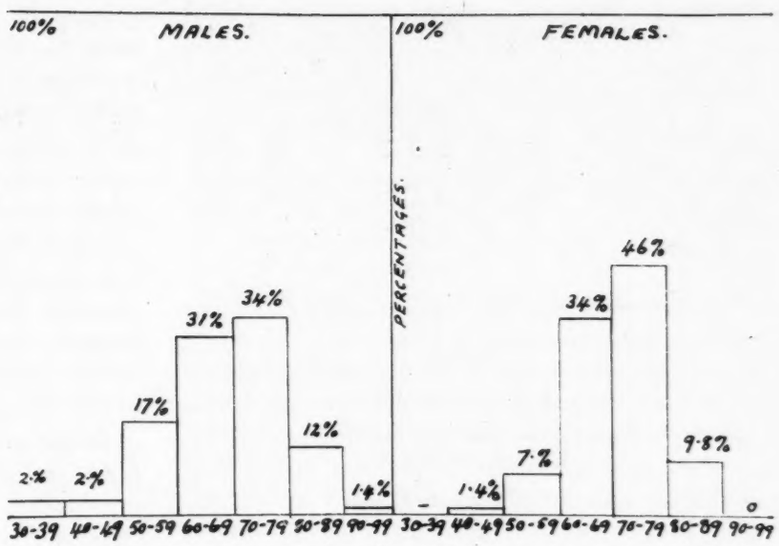

Fig. 1.—Percentages of myocardial infarctions by age groups in each sex.

TABLE I.—AGE DISTRIBUTION OF THE POPULATION OF VICTORIA CITY AS COMPARED WITH THAT OF ALL CANADA.

	Victoria City 1951 census Populations	
	Male	*Female*
Total	24,075	Total 27,256
Ages	*Percentages*	
60 - 64	6.65%	6.04%
65 - 69	7.32%	6.04%
70 - 74	5.79%	5.19%
75 - 79	3.09%	3.36%
80 - 84	1.44%	1.79%
85 - 89	0.53%	0.63%
Total	24.82%	23.05%
All Canada		*1951 census*
Total	7,088,873	6,920,556
Ages	*Percentages*	
60 - 64	3.73%	3.49%
65 - 69	3.22%	2.97%
70 - 74	2.26%	2.23%
75 - 79	1.33%	1.36%
80 - 84	0.65%	0.73%
85 - 89	0.25%	0.32%
Total	11.44%	11.10%

Sex and age of the patients were compared, as well as the percentages of cases in both males and females, occurring in ten-year age groups from 30-39 to 90-99 (Fig. 1). These data, in turn, have been related to the population characteristics of the area from which the cases were drawn.

In addition, observations were made in regard to signs and symptoms of infarction, hospital course, laboratory correlations, associated diseases present, and those cases autopsied.

Electrocardiograms taken will be discussed separately, and in some detail.

RESULTS

Fig. 1 presents the percentages of cases, in both males and females, occurring in 10-year age groups, from 30-39 to 90-99. It was found that 67.5% of cases occurred in males, with the peak incidence of 71% of the cases between 60-80 years of age; 32.5% were in females, the peak incidence occurring in the same years. The average age of the females in the group is 70 years, while the average for males is slightly but not significantly different, from a statistical standpoint, at 63 years. Although the over-all average ages for males and females do not differ significantly, it will be noted that the proportionate increase in numbers of cases, for certain age groups, as between males and females, is quite different. This difference in proportionate increase between males and females is significant at the 1% level between 50-59 and 60-69, but is not significant at the 5% level between 60-69 and 70-79, or 70-79 and 80-89.

Table II lists the predominant signs and symptoms in this group of cases. As expected, crushing retrosternal chest pain was the predominant complaint in 75% of the victims; painless infarction was specifically recorded in 19 cases—roughly 9%. All such cases showed

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TABLE II.—PREDOMINANT SIGNS AND SYMPTOMS FOUND IN THE SERIES OF CASES STUDIED.

Symptoms	*No.*	*%*	*Signs*	*No.*	*%*
Chest pain	144	76%	Shock and/or collapse	80	42%
Short of breath	48	25%	Failure	63	33%
Vomiting	19	10%	Cyanosis	21	11%
Chest tightness	11	6%	Sweating	19	10%
Cough	4	2%	Pallor	4	3%
Back pain	1	0			

other evidence of infarction. In eight cases infarcts were demonstrated at autopsy; 11 cases showed unequivocal E.C.G. changes, of which eight were indicative of anterior, two of septal, and only one of posterior infarction. The interest of physicians, generally, in painless myocardial infarction was very apparent, such an occurrence being recorded specifically in the above cases. One cannot be certain, of course, that all such cases are included in the above number. It was felt from study of histories and charts that in more than half of such incidents the awareness of pain might well have been related to the degree of shock present, as well as to its suddenness of onset. Many of the patients, of course, had multiple symptoms and/or signs.

Sixty-four per cent of the charts either did not mention associated disease or included minor irrelevant conditions. Hypertension and diabetes mellitus were by far most frequently mentioned in the remaining 36%. Of infarctions occurring in the immediate postoperative period, an interesting group of seven occurred after prostatectomy. Single cases occurred after other operations, including amputation and cholecystectomy. One very interesting case occurred in a post-lobotomy patient, and it is noteworthy that he complained of severe, distressing, retrosternal chest pain. In 20 instances, charts specified that cardiac infarction had occurred previously one or more times in the same patient; in 15 cases, the patient was being observed in a second attack, and in 5 cases, in a third attack. Of these last five, one lived and four died.

ELECTROCARDIOGRAMS

In 80 of the 218 patients accepted for the study, using the criteria outlined above, an electrocardiogram was not available for analysis. Upon critical analysis, 27 of the remaining 138 tracings, or in round figures 20% of tracings, did not give a clear-cut electrocardiographic picture of acute cardiac infarction. Sixty per cent of all tracings in the study were taken as leads I, II, III, V2, V4, and V5, and 40% were recorded with leads I, II, III, AVR, AVL, AVF, V2, V4, and V5. Sixteen of the 27 non-specific E.C.G. tracings were found in the group in which no limb leads were taken.

These 27 tracings mentioned above exhibited various patterns, as follows: (1) non-specific changes, 10 cases; (2) left ventricular strain, 2 cases; (3) digitalis effect, 5 cases; (4) auricular fibrillation, 5 cases; (5) various types of block, 5 cases.

Under group 1, "Non-specific changes", have been included tracings showing evidence of myocardial anoxia, either from coronary insufficiency or other cause, in which it was felt definite evidence of infarction could not be seen. Fifty-seven per cent or 73 of the remaining tracings showed changes involving the anterior wall, distributed as follows: anterior infarction only, 33 cases; anterolateral infarction, 19 cases; anteroseptal infarction, 15 cases; anteroposterior infarcts, 6 cases.

Fifty-five tracings located the infarct posteriorly. Of the 80% of cases showing a clear-cut infarction pattern, arrhythmias occurred in practically every case, if auricular and ventricular extrasystoles are included; 25% of these cases developed other types of arrhythmias, as follows: bundle-branch block, 16% (right slightly more frequent than left); auricular fibrillation, 8%; intraventricular block, 6%; paroxysmal auricular tachycardia, 2%; atrioventricular block, 5%; ventricular tachycardia, 2%.

Three cases with serial tracings are particularly interesting, since over variable periods of time, up to 16 days after the acute illness, they gradually evolved a clear-cut infarction pattern.

The hospital course of 190 cases was studied, 28 cases being rejected for this analysis on the grounds of inadequate records. The mortality in the group was unexpectedly high at 61.5%, and the autopsy rate was disappointingly low at 19%. Sixty-two of the patients showed signs of heart failure, according to their charts, and of these, 50 died—30% on the first day; three-quarters of the deaths occurred in the first two weeks. Sixty-nine per cent of all females died of their acute infarction, whereas this was true of only 57% of males.

It was felt that the wide scatter of clinical and laboratory data in a study of this type made detailed statistical correlation meaningless. From the data collected, however, one relationship became quite apparent—this is shown in Table III. As noted by others, the mortality from myocardial infarction rises sharply as the white cell count tops 20,000. In this connection one case is of particular interest. His white cell count was recorded at 34,000, and at autopsy more than 50% of the total amount of myocardium was infarcted.

TABLE III.—RELATIONSHIP BETWEEN WHITE CELL COUNTS AND SURVIVAL OF THE PATIENTS.

W.B.C.	*Lived*	*Died*
5-7999	6	4
6-9999	7	3
10-12999	15	13
13-15999	12	10
16-18999	8	10
19-21999	1	10
Above 22	0	2

Pathological examination brought to light 32 separate infarcts, plus four cases which showed two or more infarcts each. Of the separate infarcts, 15 occurred in the septum, 13 were placed anteriorly and only four posteriorly. Two cases of myocardial rupture were encountered.

Of the 27 cases showing E.C.G. changes interpreted as being non-specific, six cases were autopsied; four of these showed recent infarcts, all located at the base of the interventricular septum. Three cases showed old infarcts, apical, interventricular, and left ventricular, and one case showed a recent localized anterior infarct.

Pertinent clinical data on these autopsied cases follow:

CASE 1.—W.H. An electrocardiogram was taken several hours after admission of a 64-year-old white male in acute pulmonary œdema, and after the intravenous administration of 1 mg. of Digitoxin. Several explanations are possible here for some S-T segment abnormalities, which were not specific for infarction.

Autopsy disclosed an old interventricular septal infarct, as well as a new infarct, on the right side of the interventricular septum, near the base.

CASE 2.—J.A. This 77-year-old male complained of nausea, vomiting, and bouts of hiccup for a week before admission. He went steadily downhill to his death the day following hospitalization, in spite of supportive treatment, including full doses of Digitoxin intravenously.

At autopsy, an old interventricular septal infarct, and a recent infarct, involving the anterior aspect of the wall of the left ventricle were noted. The electrocardiogram was compatible with coronary insufficiency and cardiac irritability.

CASE 3.—J.N. This 72-year-old white male had fainted two weeks before admission and had been intermittently confused and dyspnœic since then. Over a three-week period in hospital, he went gradually downhill to his death. At no time did he complain of chest pain.

At autopsy, a diffuse area of fibrosis was described at the apex of the heart, in addition to a recent infarct 0.5 cm. in diameter at the base of the interventricular septum. Electrocardiogram suggested diffuse myocardial damage.

CASE 4.—A.D. This 79-year-old woman had suffered for years from rheumatic mitral stenosis, with periodic bouts of shortness of breath. She was heavily digitalized but was finally admitted in congestive failure, from which she failed to recover.

Old and recent myocardial infarction, recorded at autopsy, was scattered throughout the wall of the left ventricle, in patches approximately 1.0 cm. in diameter. Her tracing suggested diffuse myocardial damage, but was not helpful in delineating recent infarction. Digitalis effect was also noted.

CASE 5.—C.T. This 82-year-old male was admitted to hospital as a case of recent myocardial infarction, after two separate attacks of severe precordial pain. He appeared shocked on admission, but slowly improved for 10 days, when he suddenly expired. The tracing taken on admission was identical to that taken one week later. A stable pattern of right bundle branch block, and lack of serial changes, did not lend electrocardiographic support to the clinical diagnosis, although it did indicate the presence of severe myocardial damage.

Autopsy confirmed the clinical diagnosis, demonstrating a recent, large interventricular septal infarct, with extension to the anterior wall of the left and right ventricle.

CASE 6.—M.K. A 66-year-old white woman known to have portal cirrhosis and anæmia complained of severe right-sided chest pain and left shoulder tip pain three days before she died, jaundiced and dyspnœic. The electrocardiogram recorded high T waves in the V leads. A yellowish, recent infarct was found in the interventricular septum, near the base of the heart, about one-half inch (1.25 cm.) in diameter.

DISCUSSION

Comparison of age, sex and mortality data presented here, with other reports, is of some interest. Levine[1] also quotes a sex incidence

of about 3.5 to 1 in favour of males, with a peak incidence, however, in the 60-69 year group. Females accounted for only about 7% of the total cases in Jacobs's[2] series. Conner and Holt[3] noticed that 75% of their patients suffered their initial attack before the 61st year.

In the group of 500 patients studied by Masters, Dack and Jaffe,[4] 77.4% were men and 22.6% women, but the average age for all their patients was 55 years—about a decade younger than the group here reported. Two-thirds of all the patients they studied fell between the ages of 45 and 65. When the number of attacks was correlated with the census of the general population in each age group, there was a progressive rise in the incidence of attacks with advancing age, to a peak at 74 years. Our own experience with an older population confirms the impression that myocardial infarction in females tends to occur over a later, somewhat more restricted age range than is the case with males. The unexpectedly high mortality rate in this group substantiates too the observation of Masters *et al.*[4] that the mortality rate varied with age, increasing gradually to the age of 59, but rising sharply thereafter.

In suggesting a cause for the occurrence of myocardial infarction in an unusually late age group in Victoria, one naturally turns to the population whence such cases are derived. In Table I, population figures in terms of Canada and of Victoria city proper (as distinct from the Greater Victoria Urban Area) are presented as percentages; surprisingly Victoria itself has over twice as many males and females between the ages of 60 and 80 as the national average. Approximately 25% of all males in Victoria are between the ages of 60 and 89. Similar figures, unfortunately, are not available for the other municipalities and for the unorganized territory in the capital region, but it is known that two-thirds of the population increase here since 1941 is due to immigration, and that more people are settling in town than in the rural areas. With all municipalities reported, this trend might well be even more marked.

While electrocardiographers may criticize the suggestion that electrocardiograms are non-confirmatory of cardiac infarction in as great a number of cases as 20%, it is emphasized that this presentation is merely intended as a study of the day-to-day diagnostic efficiency of the electrocardiogram in infarction as it is ordinarily used by the medical profession. Doubtless several, at least, of the non-specific tracings reported in the group would have shown typical infarction patterns developing over a period of days if serial tracings had been done. In this respect, the electrocardiograph follows the usual pattern of laboratory aids, with the diagnostic efficiency and value of data obtained being augmented appreciably by serial records over a period of time in the disease.

SUMMARY

1. A study of 218 selected cases of acute myocardial infarction is presented.

2. Sex incidence agrees with other reports of similar groups of cases; age incidence is quite different, however, and is shown to be related to the general population characteristics of the area from which the cases derive.

3. Routine hospital electrocardiogram diagnose about 80% of cases of myocardial infarction.

4. The mortality rate of 61.5% prevailing in this group of cases is much higher than in previous reports.

5. In this series right bundle branch block was at least as frequent a complication of acute myocardial infarction as left.

CONCLUSIONS

1. Myocardial infarction in women occurs in a later, more restricted age range than in men, and tends to be more lethal. Peak incidence occurs through the same age group in both sexes.

2. Conclusions reached previously in regard to age incidence of myocardial infarction, through statistical correlation, are confirmed in this study, actually carried out on cases from an older age group.

3. Routine electrocardiogram diagnose about 80% of all acute myocardial infarcts. They are most efficient as diagnostic tools when fresh infarcts occur in relatively healthy hearts. Old infarcts are often missed, electrocardiographically; when the myocardium is repeatedly insulted by atherosclerosis, electrical differentiation of fresh, from old, infarction becomes increasingly difficult.

4. Infarcts located at the base of the interventricular septum would appear to be quite frequently missed electrocardiographically.

The record staffs of the three hospitals were very helpful in providing the necessary charts and electrocardiograms.

Mr. L. Spencer, in charge of the Department of Medical Photography, St. Joseph's Hospital, Victoria, B.C., did the line drawings.

Professor G. W. Manning, London, Ont., very kindly read and criticized the manuscript.

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REFERENCES

1. LEVINE, S. A.: Clinical heart disease, 3rd ed., W. B. Saunders Company, Philadelphia, 1945.
2. JACOBS, T. P.: *Ann. Int. Med.*, 34: 114, 1951.
3. CONNER, L. A. AND HOLT, E.: *Am. Heart J.*, 5: 705, 1930.
4. MASTERS, A. M., DACK, S. AND JAFFE, H. L.: *Arch. Int. Med.*, 64: 767, 1939.

RÉSUMÉ

L'auteur a choisi 218 cas d'infarctus aigu du myocarde venant d'une population dont l'âge moyen est de beaucoup supérieur à celui du reste du pays. La distribution entre les deux sexes est à peu près la même que celle qu'on a déjà rapportée antérieurement. D'après son expérience, les électrocardiogrammes de routine dans un hôpital ne peuvent aider à diagnostiquer qu'environ 80% des cas d'infarctus. Parmi les complications qui suivirent, le bloc de branche droit fut aussi fréquent que celui de gauche. La mortalité de cette série qui s'élève à 61.5% s'explique par le grand âge de la plupart des malades.

Case Reports

ISLET CELL TUMOUR IN DIABETES MELLITUS: REPORT OF TWO CASES*

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THE CURIOUS and paradoxical association of a functioning islet cell tumour in the pancreas of a man with long-standing diabetes mellitus is the subject of this report. An additional case of a non-functioning adenoma in a diabetic is reported.

CASE 1.—J.M., male, aged 53 years. This retired veteran initially came under the care of the Department of Veterans Affairs in May 1951. It was known that he had suffered from diabetes mellitus for 11 years previously but very little was known of control up to that time. There was no family history of diabetes. He was alert, oriented and well-nourished. Physical examination was normal. The blood pressure was 150/80. His fasting blood sugar was raised as high as 250 mg. %. His non-protein nitrogen (N.P.N.) was 35 mg. %. Repeated urinalyses were negative apart from occasional glycosuria but no acetonuria. During this admission it was reported repeatedly that the patient was extremely difficult to control as he would not adhere to his diet, and he went into apparent insulin reactions with remarkable ease. In the interval between May and September 1951, he had 14 hypoglycæmic reactions of varying severity from mild confusion, dizziness, sweating, tremor, incoherence and ataxia, to coma, occurring at various times throughout the day and night, with blood sugar levels as low as 30 mg. %. On these occasions he required 40-50 c.c. of 50% glucose intravenously to regain consciousness. On one occasion he was unconscious for two hours. He was discharged after six months on a 2000-calorie diet and 50 units of globin insulin each morning.

His second admission was in January 1952, when he was in hospital for five weeks, having many hypoglycæmic reactions at peculiar times, as previously. They would occur before or after meals, or during the night. One of several blood sugar readings was 25 mg. %. He was seen by a psychologist, who concluded that he was a "dull normal" individual. His blood pressure had risen to 150/100.

He was not seen again until two years later, when he re-entered hospital in March 1954, complaining of frequent attacks of diarrhœa and blurred vision. He was having frequent hypoglycæmic symptoms as before and these recurred about five or six times a week, mostly between 6.00 and 7.00 a.m. He was taking 20 units of protamine zinc insulin every morning. He now showed an early diabetic retinopathy with scattered Ballantyne aneurysms in both fundi. A Grade III apical systolic murmur was heard which was localized, and decreased arterial pulsation was noted in his lower limbs. His fasting blood sugar ranged from 45 to 390 mg. %; serum cholesterol was 325 mg. %; total serum proteins were 6.2 g. %; albumin 3.5 g. %; globulin 2.8 g. %. He was discharged after eight weeks on a 1700-calorie diet and 25 units of protamine zinc insulin each morning.

He remained comparatively well until September 1954, when he had another hospital stay of seven months with bilateral pyelonephritis, which was extremely refractory to treatment. He also complained of retrosternal gripping pain of anginal type. Femoral arterial pulsations were diminished bilaterally, and pulsation was absent in the feet. His diabetic retinopathy had progressed, and for the first time there was evidence of diabetic neuro-

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pathy with absent vibration and position sense below the knees. Urine albumin output was 11.5 g. % in 24 hours. His insulin was reduced to 10 units of protamine zinc insulin daily and he experienced many hypoglycæmic reactions in the early morning, with blood sugar levels as low as 38 mg. %. He developed mild left ventricular failure, which was easily treated by salt restriction, mercurial diuretics and digitalis leaf. His diagnosis was diabetes mellitus with secondary Kimmelstiel-Wilson disease, retinopathy and neuropathy.

His final admission was on March 1, 1956. He was euphoric and fatuous. There was gross pitting œdema of both legs as high as the knees and he had a gangrenous area over the medial side of the right big toe. The femoral pulses were barely palpable and no other pulses were felt in the legs. Apart from his mental deterioration, no further change in his central nervous system was noted. Fasting blood sugar varied from 32 to 400 mg. %. On March 11, 1956, he was given his usual insulin dose (10 units of protamine zinc insulin) in the morning and one-half hour later he became drowsy and confused, and was sweating and disoriented. His blood sugar was 44 mg. %. He responded very slowly to 100 c.c. of 25% glucose in water intravenously. His albuminuria had increased to 14 grams in 24 hours and his N.P.N. was 53 mg. %. Serum protein was 5.4 g.; albumin 3.1 g. %; globulin 2.3 g. %. He repeated these attacks four times, gradually deteriorated and died on April 6, 1956, after 16 years of diabetes mellitus complicated by intervals of severe hypoglycæmia for at least five years.

PATHOLOGICAL FINDINGS

Autopsy.—Death was due to extensive confluent basal bronchopneumonia, which was very severe in the right lung but less so in the left lung. Cultures yielded *Streptococcus pneumoniæ* and *Staphylococcus aureus.* The heart was not enlarged and weighed only 300 grams. A severe degree of atherosclerosis was evident in the medium-sized arteries. The coronary arteries were thick-walled and tortuous, with changes extending even into the small branches. The atheromata were patchy and nodular, eccentrically placed, stenosing the lumina to small crescents but not to complete occlusion. The renal and mesenteric arteries, and cœliac axis and its branches were similarly involved by severe atherosclerosis. The aorta was remarkably free of disease. The kidneys were large and œdematous, each weighing 240 grams, with prominent bulging, pale cortices and very fine indefinite cortical granulation. Microscopically, there was found a well-advanced nodular glomerulosclerosis typical of that occurring in diabetes mellitus (Fig. 1). The lesions consisted of globular deposits of eosinophilic hyaline material, positive to the periodic acid-Schiff (P.A.S.) reaction, lying within the tufts of the glomeruli and often outlined by a circle of capillaries. Advanced lesions converted glomeruli into solid hyaline masses. Arterioles in kidneys, as in other organs, were severely sclerosed by deposits of hyaline, P.A.S.-positive material.

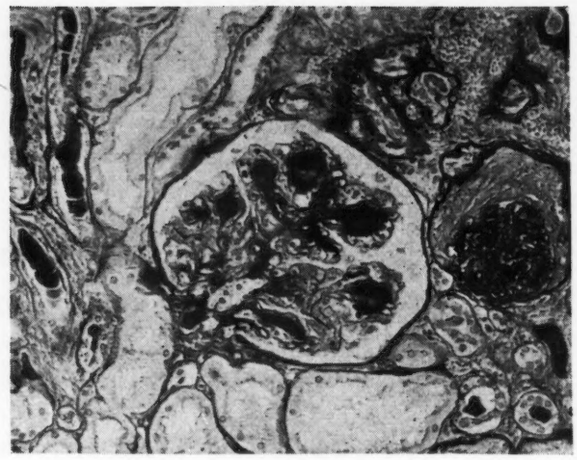

Fig. 1.—Diabetic glomerular sclerosis in Case 1.

The pancreas grossly presented no remarkable change from normal. However, embedded in the head was a small pea-sized encapsulated nodule, differing in texture and colour from the rest of the gland, being pale greyish-red, soft, moist and bulging, and measuring 0.8 cm. in diameter. Microscopically, the capsule was thick, dense and well defined. The tumour was richly vascular and composed of anastomosing cords or ribbons of a fine reticulum, carrying cells two or three layers in depth (Figs. 2 and 3). Cords of cells frequently encircled capillaries. Individual cells were uniform in size and cuboidal or polyhedral in shape, poorly outlined, with a moderate amount of cytoplasm of faint basophilic staining. Nuclei were central, regular and round, with dense condensations of chromatin and prominent nucleoli. No mitoses were observed. Sections were stained by Gömöri's aldehyde-fuchsin method but beta granules could not be demonstrated.

The islets of the pancreas were little altered, the cells being arranged in cords with no evident degeneration or fibrosis. Arterioles were severely sclerosed with hyaline deposits. The acinar portion

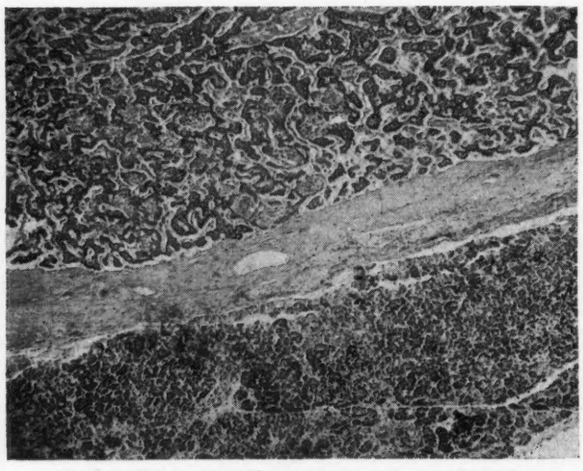

Fig. 2.—Islet cell adenoma—low power. Case 1.

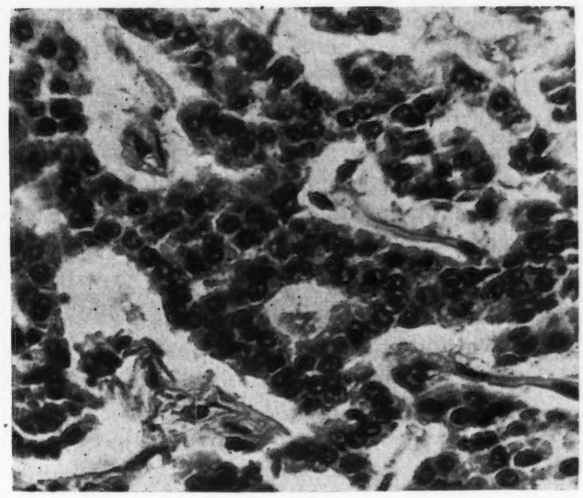

Fig. 3.—Islet cell adenoma—high power. Case 1.

of the pancreas was not abnormal and there was no compression or fibrosis surrounding the tumour.

CASE 2.—L.V.S., male, aged 72 years. After a minor trauma, this elderly man (a grocer) developed an ulcer on his ankle and foot, which progressed rapidly, exposing the tendons over a large area. He was found to have glycosuria and a fasting blood sugar of 290 mg. %, and diabetes mellitus was diagnosed. It was difficult to control the diabetes, the hyperglycæmia persisting, and only once was a normal fasting value of 84 mg. % obtained. No insulin reactions of any type were experienced. Blood pressure was not elevated. The ulcer on the foot could not be arrested; it became infected with *Staphylococcus aureus* and an amputation was performed seven weeks after the injury. A week later he had a massive rectal hæmorrhage of bright red blood and a small mucosal ulcer was found, fulgurated and the rectum packed. He received six pints of blood. No further bleeding occurred but over the next four weeks his progress was poor; he finally lapsed into a coma for six hours, with a blood sugar of 328 mg. %, and died.

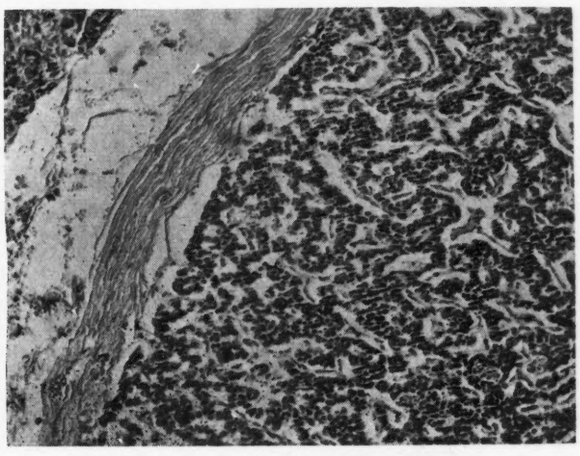

Fig. 4.—Islet cell tumour in Case 2.

PATHOLOGICAL FINDINGS

Autopsy.—An extensive bronchopneumonia due to *Staphylococcus aureus* was considered the immediate cause of death. The heart was moderately hypertrophied; the coronary arteries were slightly sclerosed. Medium-sized arteries were thick-walled and tortuous. The remaining organs were normal. By mere chance the routine microscopic section from the head of the pancreas included a small islet cell adenoma, 0.5 cm. in diameter, encapsulated and embedded deeply in the head.

The histology was identical to that in Case 1. A thick, dense compact fibrous capsule enclosed the tumour. Regular, poorly defined polyhedral cells in one or two layers formed cords often in juxtaposition to capillaries, but more often separated by a fine reticulum. Nuclei were round and flecked with dense chromatin. Occasional pyknosis was present, but no mitoses (Figs. 4 and 5). The islets in the pancreas were severely altered by fibrosis, with complete disappearance of about one-

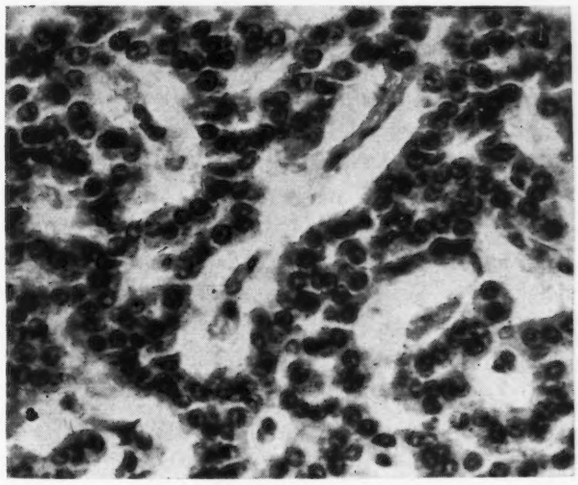

Fig. 5.—Islet cell tumour in Case 2.

half the cells of each islet, the remaining cells being either swollen or shrunken and lacking the usual cord-like arrangement.

In the kidneys was found hyaline sclerosis of terminal arterioles and slight thickening of glomerular basement membranes, but no nodular glomerular sclerosis.

COMMENT

The incidence of islet cell tumour is reported variously as 1:1000 autopsies[1] to 1:234 autopsies.[2] The capacity to function, as evidenced by hypoglycæmic symptoms, is found in only 20%[1] to 30%[3] of tumours.

The clinical triad essential for differential diagnosis proposed by Whipple[4] is (1) initiation of an attack during a 24-hour fasting; (2) a low blood sugar of less than 50 mg. % during the fasting interval or in an attack of hyper-

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insulinism; (3) recovery from an attack by administration of glucose. This triad with electroencephalographic changes led to a diagnosis of tumour in 34 out of 39 cases; the tumours were then successfully removed.

The glucose tolerance test gives variable results, and in one-half of cases results in a diabetic type of curve. The 24-hour fasting test is more reliable, and in the presence of functioning adenoma should result in a blood sugar reading below 50 mg. %, and may precipitate an attack of hypoglycæmic symptoms and coma. Porter and Frantz,[5] in a review of 43 patients with pancreatic tumours (30 benign; 13 probably malignant), again emphasized the fact that the glucose tolerance test is an unreliable investigation. They also reaffirmed the value of Whipple's triad in reaching a definite conclusion.

The existence of functioning islet cell tumours has been recognized since 1927, when Wilder[6] recorded the finding of such a tumour. Subsequent cases gleaned from the literature total over 425. Of the available literature, the only recorded case of an insulinoma in a diabetic individual is noted in a well-documented report by Van Der Sar *et al.*[7] This woman's diabetes had been controlled with diet and insulin for two years, when she developed attacks of hypoglycæmia in the early morning. Insulin was reduced but the attacks recurred over a period of another 10 years. She then reappeared in coma, and a detailed investigation pointed to a functioning insulinoma. Whipple's triad and electroencephalographic changes substantiated the diagnosis. An operation yielded a small discrete tumour in the body of the pancreas. Postoperative blood sugar rose to 570 mg. % and no further attacks of spontaneous hypoglycæmia occurred in the subsequent three years. However, mental deterioration persisted, with maniacal tendencies. Bickel *et al.*, quoted by Van Der Sar,[7] recorded the case of a severe diabetic who developed hypoglycæmic attacks from islet cell carcinoma of pancreas with metastases to the liver. This was considered a functioning tumour, as extract of the tumour injected into dogs produced insulin effects.

Concerning the present case of functioning insulinoma, the suspicion of an islet cell adenoma during life was obscured by the existence of diabetes for 16 years. The episodes of hypoglycæmia in this patient who was receiving insulin and who frequently refused his food, were ascribed to poor control, or marked lability of his diabetic state.

In retrospect, the diagnosis would seem obvious when one considers that this patient developed severe hypoglycæmic reactions in the early morning on as little as 10 units of protamine zinc insulin administered 24 hours previously. The mental confusion was probably a manifestation of the hypoglycæmic state. However, as previously noted, these were considered secondary to his exogenously administered insulin. That this man had diabetes mellitus was substantiated in life by the complicating nephropathy and retinopathy. The unique coexistence of diabetes mellitus with a functioning insulinoma was not considered.

The presence of non-functioning islet cell tumours in diabetics is not unknown. Such a case is included in this report because it occurred in close succession to Case 1. During 12 weeks' treatment in hospital, the second patient did not manifest any symptoms of hypoglycæmia. It is assumed therefore that this insulinoma was not actively functioning.

SUMMARY

The coincident occurrence of a functioning islet cell tumour in a patient with diabetes mellitus of 16 years' duration is reported. The diagnosis was made at autopsy. Retrospectively, its presence during life is obvious.

The case of a non-functioning islet cell tumour in a diabetic man is also reported.

REFERENCES

1. WHIPPLE, A. O. AND FRANTZ, V. K.: *Ann. Surg.*, **101**: 1299. 1935.
2. LOPEZ-KRUGER, R. AND DOCKERTY, M. D.: *Surg. Gynec. & Obst.*, **85**: 495, 1947.
3. HOWARD, J. M., MOSS, N. H. AND RHOADS, J. E.: *Internat. Abstr. Surg.*, **90**: 417, 1950.
4. WHIPPLE, A. O.: *J. Internat. Chir.*, **3**: 237, 1938.
5. PORTER, M. R. AND FRANTZ, V. K.: *Am. J. Med.*, **21**: 944, 1956.
6. WILDER, R. M. *et al.*: *J. A. M. A.*, **89**: 348, 1927.
7. VAN DER SAR, A. *et al.*: *Docum. med. geog. et trop.*, **8**: 85, 1956.

ALCOHOLISM

There are more than 180,000 alcoholics in Canada. The average Canadian alcoholic is a skilled or semi-skilled person between 35 and 45 years of age, and is married, with two or three children; he is employed and maintains his own home. In 1943 there were 1240 alcoholics for every 100,000 adult Canadians. In 1956 the number had increased to 1850 alcoholics for every 100,000 adults.

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PENICILLIN ANAPHYLAXIS* A CASE REPORT AND SOME NOTES ON ITS PREVENTION

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MY MAIN REASON for reporting this very unfortunate case is to record yet another incident of a fatal penicillin reaction. I hope that in doing so I shall again call attention to the occasional very serious toxic reactions of a widely used therapeutic drug. Penicillin is probably our most commonly used antibiotic, and it is well to remember that while serious and occasionally fatal reactions are very rare they do occur.

The less serious and comparatively common penicillin allergies are seen quite frequently in practice. The acute anaphylactic type of reaction is generally thought to occur in individuals who have had a previous less serious reaction, but this case proves that such is by no means the rule.

I performed a simple submucous resection of the nasal septum on R.H. (a young healthy male, aged 20 years) on July 26, 1956. He had never had any previous serious illnesses.

The following day he had a temperature of 99.6° F. (orally). To prevent any sinusitis, I ordered 800,000 u. of Duracillin (penicillin-G procaine plus penicillin-G sodium) to be followed by 400,000 u. b.i.d. This was to be given by intramuscular injection. Previously I had removed his nasal plugs, which I do routinely 24 hours after operation.

At 12 noon, two hours after he received his injection, I was urgently called to see my patient. Apparently the nurse had just noticed his critical condition. I have never seen anything quite like his condition. He was quite conscious and responsive, his colour was a slate-like bluish grey, there was no apparent respiratory obstruction, blood pressure and pulse were imperceptible, heart sounds were barely audible, central nervous system and ocular fundi were normal. He was obviously in a state of acute circulatory collapse. He immediately received the following therapy:

1. Continuous oxygen by mask.
2. Vasoxyl 1 c.c. intravenously.
3. Coramine 5 c.c. intravenously.
4. An intravenous drip was started and the following drugs were given in 1 litre of 5% dextrose: (a) 5 c.c. l-norepinephrine (Levophed). (b) 20 units ACTH (Duracton). (c) 100 mg. hydrocortisone.
5. A second intravenous drip was put up in another vein and 500 c.c. of dextran started.

In view of the fact that he was getting Levophed, I saw no point in giving any adrenaline. He did, however, receive adrenaline later on that day in two separate doses of 0.5 c.c. each, with no obvious beneficial effect.

The intravenous drips were run quite rapidly at first. One hour later his condition was improving somewhat. Systolic blood pressure was perceptible at 60; diastolic could not be determined; the pulse rate was 140. His condition remained more or less static for the rest of that day (July 27). Colour with oxygen was fairly good. He had recurrent attacks of vomiting and hiccups.

Between midnight on July 27 and 10 a.m. on July 28 he received 10 c.c. of Levophed in 2000 c.c. of 5% dextrose, 500 c.c. of dextran and 1500 c.c. of plasma.

I realize that our therapy was somewhat varied and perhaps empirical, but we regarded it as at least the best we could do in a desperate situation.

By 10 a.m. on the morning of July 28 he was much better; colour was good without oxygen. Blood pressure was 104/70, pulse 100. The actual improvement commenced during the early hours of July 28 and continued gradually up to 10 a.m. It was found that the dose of Levophed necessary to maintain a satisfactory blood pressure fell quite rapidly during the early morning hours and it was possible to discontinue it altogether at 10 a.m. on July 28.

The patient's temperature at 12 noon on July 28 was 98° F. (previous afternoon 103° F.). At that time there were several factors to consider. His initial condition was not at all typical of anaphylaxis, the reaction did not occur for two hours after the penicillin injection (as far as I know most of the recorded penicillin reactions have occurred immediately after the injection), and he had had an operation. Could this have been an acute overwhelming infection? It is well known that such an acute state of shock can occur in the latter condition. On the afternoon of July 27 he was therefore put on 1 g. of chloramphenicol by intramuscular injection b.i.d.

In order to help maintain the condition noted at 10 a.m. on July 28, he was put on cortisone 25 mg. q.4.h. in tablet form, and Phenergan 50 mg. b.i.d. by intramuscular injection. The latter was thought to be a useful drug in this situation because the patient was somewhat restless and agitated. Later that day, because of intermittent vomiting, the crushed cortisone tablets were administered per rectum. During the day of July 28 his condition remained more or less static. He had occasional attacks of vomiting and hiccups. As it was thought inadvisable to give any fluids orally in view of his vomiting, the following solutions were ordered for intravenous administration during the day of July 28: 1000 c.c. of Electrolyte Number 2 (Baxter), 1000 c.c. of normal saline, and 1000 c.c of 5% dextrose. He subsequently received all of these.

At 6:30 a.m. on July 29, he suddenly seemed to go downhill, his general condition deteriorated,

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cyanosis returned, the pulse rate rose rapidly, and blood pressure collapsed, while breathing became very noisy. The patient obviously had acute pulmonary œdema, and a recurrence of his original circulatory collapse. This was confirmed by examination. He vomited several times and became quite restless and unmanageable (it took three people to keep him in bed). At approximately 7 a.m. he went into coma and died shortly afterwards.

Later that day I performed an autopsy. All organs were normal apart from the lungs. The bronchi were full of a frothy bloodstained fluid and the lungs were sodden with fluid. The picture was one of acute pulmonary œdema. The operation site was quite normal, as was the floor of the anterior cranial fossa. The pituitary, the adrenals and sections of the lungs, heart, spleen, liver and kidneys were sent for pathological examination. All were normal, apart from the lungs, which showed acute pulmonary œdema. I might add that throughout this man's illness he had a satisfactory urinary output.

This patient had not received any previous parenteral penicillin. He did, however, receive a topical penicillin preparation for impetigo of his chin in 1948 (at that time the dangers of local penicillin therapy were probably unknown). He had an acute urticaria of unknown origin in 1947 and eczema as an infant. He also had a rash of unknown origin (probably eczema) on his right forearm in 1951. As far as I could find out, he had no local reaction to the topical penicillin he received in 1948.

My patient was a muscular young man in excellent physical condition. To this I attribute his survival for so long after his initial collapse. His age and condition (and I suppose the nonessential administration of penicillin) also add up to make this a very unfortunate case.

Anaphylactic penicillin reactions are becoming increasingly common, and I feel that before any patient is given penicillin either orally or parenterally the following facts should be considered:

1. Has the patient had a previous reaction to penicillin?

2. Has the patient a personal history of allergy?

3. Perhaps even a strong family history of allergy should be considered a contraindication?

Furthermore, as these reactions are becoming more prevalent and more widely known, this whole question may well have medico-legal facets.

Penicillin should never be used topically. Apart from the possible danger of sensitizing a patient to subsequent parenteral or oral doses of penicillin, I think that it is nowadays generally agreed that the high percentage of local allergic reactions to penicillin and sulfonamides is very much against their being used locally. Furthermore, why use an antibiotic locally and thereby possibly cultivate resistant strains of bacteria against its possible subsequent parenteral administration for serious infections? There are antibiotics available too toxic for systemic therapy but excellent for local therapy, because of their broader spectrum and comparatively rare production of allergic reactions. Combinations of the latter are now being widely used.

This case also presents another problem. Why did the patient seem to recover and then deteriorate later on? He lived for almost two days. Since his heart appeared normal at autopsy, I suppose it is reasonable to assume that the pulmonary œdema that was the immediate cause of death was secondary to pulmonary vascular lesions of anaphylactic origin. Is it possible that when the patient's circulation improved, he absorbed more penicillin and started the whole anaphylactic process all over again? An associate of mine suggested this, and I feel that there may well be something in it. The length of time between the initial reaction and the later collapse of the patient is possibly against such a theory in this case. Another associate of mine has encountered a more recent acute penicillin reaction; in this case, which was not quite so severe as mine and in which recovery was rather rapid, the area of the injection was incised and allowed to bleed freely. It is possible that this helped; theoretically at least, it seems a good idea in acute penicillin reactions, especially when a long-acting penicillin preparation is responsible. Another of my associates has seen an acute anaphylactic reaction to oral penicillin. In this case the patient also recovered. In such a case one has more control over the situation and can institute stomach washouts to get rid of at least some of the penicillin.

Any patient who has had a minor penicillin reaction should be informed of the dangers of subsequent penicillin therapy. This might prevent his getting any more penicillin, as in my experience most doctors mention to patients beforehand what drugs they intend to give them. This is probably more true of office than hospital

practice, where the physician is more liable to order drugs in the patient's absence. If any of my patients tell me that they have had a previous penicillin reaction or get one as the result of my therapy, I write "PENICILLIN SENSITIVE" across their chart cover in large letters to prevent any subsequent penicillin therapy in our group. I feel that we should constantly be aware of the possible dangers of penicillin, because I can certainly visualize how easily penicillin may be given to the wrong patient, especially in the middle of a busy session.

Anaphylactic reactions are undoubtedly far more common with parenteral than with oral administration of penicillin, and an increased use of the latter route might help to prevent them. This practice, while a good one, might be expensive if adequate blood levels are to be secured for a sufficient length of time; apart from the expense, in serious infections it is still considered advisable to use parenteral rather than oral administration of penicillin.

If it is imperative to use penicillin in a potentially dangerous situation (and frankly I cannot visualize this, because there are other antibiotics available that do everything penicillin does and often more), it would seem advisable to give 0.1 c.c. intradermally and wait for 30 minutes to observe any allergic reaction. This may have a place in treating patients who have or have had allergy in one form or another, and need an antibiotic for a current infection.

It is also well to remember that acute anaphylactic reactions and the other more common allergies can apparently occur with other antibiotics. Those, however, appear to occur far less commonly than with penicillin. Perhaps at a later date, when they have been used on as many patients and as often as penicillin, allergic reactions to them may become more prevalent. At one time acute anaphylactic reaction to penicillin was unknown, although it was being freely used. Some years ago the occasional case began to appear in the literature.

The inclusion of an antihistamine in penicillin for injection has been advocated. Chlor-tripolon is the one most commonly used. I remember reading about one series of cases where this practice had proved to be beneficial. A short time later I read that another investigator had conducted a similar trial and decided from his results that it was of little or no value.

Perhaps adrenaline, if given immediately to my patient, might have been of some benefit, and no doubt it should always be immediately available if penicillin is to be administered to any patient. I must confess, however, that because of the previously mentioned factors involved in this case, I did not immediately think of the likelihood of a penicillin reaction; when this did ocur to me I had already given l-norepinephrine and at that time I presumed that it had done anything that adrenaline could have done. Perhaps that was not a correct assumption on my part? Later on, adrenaline was given, with no beneficial results, but I suppose that this was a bit late for a fair trial of the drug. I am aware that adrenaline has worked many times in acute penicillin anaphylaxis and is probably the drug of choice for the initial treatment of such catastrophes.

SUMMARY

A case of acute anaphylactic shock after penicillin injection is reported. The treatment adopted is outlined, and some impressions are presented on how such catastrophes might be avoided.

ATTENUATION OF CHICKENPOX WITH GAMMA GLOBULIN*

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Youngstown, Ohio

THE RECENT DEATH from generalized varicella of a member of the intern-resident staff of St. Elizabeth Hospital, Youngstown, Ohio, has been the occasion of an inquiry into agents that could be utilized on a preventive, attenuating or therapeutic basis to protect contacts. Investigation revealed a paucity of reports concerning the use of agents of proven value in this regard. Ascorbic acid, para-aminobenzoic acid and Protamide[1] have been proposed as being effective in therapy. Immune globulin has been reported[2] as possibly having attenuated the skin lesions of chickenpox. Observations of a similar nature with respect to gamma globulin made in

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a group of hospital interns form the basis for this report.

Most physicians and laymen view chickenpox as a mild disease, and probably would not be receptive to the idea that there is a need for a prophylactic agent for it. However, in the past year a number of reports[3-8] have emphasized the fact that chickenpox can indeed be a very serious disease, and that a fatal termination is not a rare event, particularly when complicated by a primary varicella pneumonia. It has fallen to our lot to be placed in a position to confirm this.

The case in point was a Filipino intern, aged 26, who was hospitalized on January 12, 1957, with a two-day history of symptoms of chickenpox and who died on January 17. Due to his having been in close contact with a number of other Filipino interns, who had no previous history of having had chickenpox, considerable anxiety arose among the house staff and the attending staff, associated with speculation as to the possible outcome of other cases should they occur. Then followed the development of three additional cases among the house staff as described below.

The first patient, aged 33, was hospitalized on January 16, 1957, having manifested skin lesions for one day and constitutional symptoms for two days prior to admission. He ran a markedly febrile course for the first three days and had a moderately severe rash characterized by numerous typical varicella skin lesions scattered over the body, but more concentrated on the face, scalp and anterior chest. These findings were confirmed by the patient's physician, Dr. S. Gaylord, and by the author. This patient had not received gamma globulin before the development of his illness.

Shortly after his admission, a considerable discussion ensued relative to the merits of gamma globulin both for therapy of the patient and for protection of the contacts. After much inquiry it was decided that gamma globulin should be administered to the patient, and moreover should be made available to all contacts on the house staff. Some dissenting opinion, including that of the author, was raised against its use on the basis of there being little or no evidence supporting its effectiveness in the prevention of chickenpox. This contention was overruled by a larger body of opinion supporting the use of the globulin, if only on an empiric basis for psychotherapeutic effect. In addition, some felt that theoretically the globulin might contain some antivaricella protective bodies, and that in any event no harm was likely to result. That this latter opinion concerning the harmlessness of globulin is not entirely valid has been pointed out by Good.[9]

On January 18, 1957, gamma globulin (Poliomyelitis immune globulin (human) – Squibb) was administered to the various members of the house staff identified as susceptibles, in a dosage of 1 c.c. per 10 lb. of body weight, the total amount being given in two divided doses, one in each buttock intramuscularly.

On January 23, 1957, the second patient, aged 29, was hospitalized with the complaints of malaise for one day and some pruritic lesions on the back for several hours prior to admission. When examined by his physician, Dr. David Levy, and by the author, he displayed lesions typical of chickenpox. Of interest was his clinical course, fever only on the day of admission (reaching a peak of 100° F.) and on the next day (reaching a peak of 99.2° F.). The rash during the entire course of the illness was very sparse, there being a total of 6 or 7 lesions in all, with the vesicles noted to be smaller and crusting more rapidly than normal.

This patient had received 13 c.c. of gamma globulin on January 17, 1957 (a day before the other housemen received their injections). In addition, he received on January 24, shortly after admission, 15 c.c. of a convalescent serum, prepared in the hospital laboratories from the blood of donors who had had chickenpox within the preceding few weeks and who had come forward as volunteer donors upon the invitation of several of the staff pædiatricians.

On February 1, 1957, the third patient, aged 29, was hospitalized with the complaints of malaise and rash of 12 to 24 hours' duration. The skin lesions when examined by his physician, Dr. James Birch, and by the author were considered typical of chickenpox. During the entire time of his illness this patient had 10-20 lesions in all, distributed over his entire body generally, including his scalp, with three to five of the lesions noted to have been vesicular. He was febrile during the first two days, a peak of 99° F. on the first and 98.8° F. on the second. This patient had received 13.5 c.c. of gamma globulin on January 18, 1957.

The two latter cases here described are without a doubt the mildest the author has seen in his experience over the past 11 years with about 150 adults with chickenpox in a 17-30 year age group. The fact that the two mild cases were the ones treated with gamma globulin appears to be more than coincidence. Obviously one is not justified in drawing valid conclusions on the basis of such a small group of patients; however, the sequence of events does seem to point up some significant facts in need of confirmation.

It was therefore felt imperative, in view of the increasing awareness of the serious potentialities of chickenpox, to bring this information to the profession without delay, directing it particularly at the general practitioner. The family physician undoubtedly would be in the best position to contribute the additional observations necessary to confirm or disprove the findings herein reported concerning the seemingly beneficial effects of gamma globulin in attenuating or possibly preventing chickenpox.

SUMMARY

Four cases of chickenpox in a hospital intern staff were observed over a period of three weeks. Two of the patients had received gamma globulin about a week before the development of clinical symptoms and ran unusually mild clinical courses. Of the other two who had not received gamma globulin, one died and the other ran the typical moderately severe clinical course noted in a young adult with chickenpox.

REFERENCES

1. LEHRER, H. W., LEHRER, D. R. AND LEHRER, H. G.: *Ohio M. J.*, 47: 44, 1951.
2. RODARTE, J. G. AND WILLIAMS, B. H.: *A. M. A. Arch. Dermat.*, 73: 553, 1956.
3. Children's Medical Center, Boston, Massachusetts, Clinical Pathological Conference, edited by S. Farber and J. M. Craig: *J. Pediat.*, 50: 212, 1957.
4. BLATTNER, R. J.: *Ibid.*, 50: 258, 1957.
5. *Idem*: *Ibid.*, 50: 515, 1957.
6. FITZ, R. H. AND MEIKLEJOHN, G.: *Am. J. M. Sc.*, 232: 489, 1956.
7. COWLEY, R. G., CREW, W. E. AND HASSETT, G. R.: *Ann. Int. Med.*, 45: 518, 1956.
8. WEINSTEIN, L. AND MEADE, R. H.: *A. M. A. Arch. Int. Med.*, 98: 91, 1956.
9. GOOD, R. A. AND MARTIN, C. M.: *J. A. M. A.*, 162: 850, 1956.

SHORT COMMUNICATIONS

ACUTE STAPHYLOCOCCAL ENDOCARDITIS TREATED SUCCESSFULLY WITH TETRACYCLINE-OLEANDOMYCIN

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IT IS FELT worth while to report a case of acute staphylococcal endocarditis which responded favourably to treatment with a combination of tetracycline and oleandomycin, after failing to respond to a variety of other antibiotics.

Mrs. E., aged 41, was admitted to the Royal Jubilee Hospital, Victoria, B.C., on September 7, 1956, with vaginal bleeding of two days' duration. Her last menstrual period had been in May 1956. A day before admission she passed a fetus; on the day of admission she passed a placenta, and developed fever and chills. She had had three full-term pregnancies without difficulty. There were no serious illnesses in the past.

She did not look ill. Temperature was 100° F., and pulse 100 and regular. Otherwise, apart from the finding of the uterine fundus three to four fingers' breadths above the pubis, the physical examination was negative. The heart was of normal size and no murmurs were heard. She was given procaine penicillin 400,000 units with streptomycin-dihydrostreptomycin 0.5 g. 12 hourly, and her condition improved. After six days of therapy, treatment was changed to erythromycin 1 g. daily in divided dosage, because of the reappearance of fever and the occurrence of a purulent cervical discharge from which a light growth of *Staphylococcus aureus* was obtained. After six more days of treatment she was discharged, being asymptomatic and afebrile. She remained well for only 24 hours, and then a temperature of 100.2° F. returned. Erythromycin was resumed in the dosage which had previously been effective, but after 48 hours, when no response occurred, it was replaced by novobiocin 1 g. daily in divided dosage. After three days of this therapy, the patient was afebrile and feeling well. A day later she developed fever, chills, nausea and low lumbar backache, and she was readmitted to hospital on September 26.

She now appeared quite flushed and the skin was hot to the touch. Temperature was 103° F., pulse 118 and regular, and respirations 28. There was no nuchal rigidity. Fundi, ears, and nasopharynx were normal. Chest negative. There was a soft blowing systolic grade 1 murmur localized to the apex, but the heart was not enlarged on percussion. Blood pressure was 110/80 mm. Hg. There was no lymphadenopathy. Examination of the abdomen revealed enlargement of the area of splenic dullness to three to four fingers' breadths, but the splenic edge could not be felt. Study of the blood revealed a red cell count of 4,100,000, Hb. value 12.2 g. %, white cell count 20,850, with polymorphonuclear cells 84, band cells 11, metamyelocytes one and monocytes four. Sedimentation rate was 111 in one hour. Urinalysis was negative. Later in the day petechiæ appeared over the body. Novobiocin, 1.5 g. daily in divided dosage, and aqueous penicillin, one million units three hourly i.m., were given.

After three days of this therapy the patient was afebrile, and looked and felt better. A blood culture taken on admission produced a moderately heavy growth of *Staphylococcus aureus*, reported as being slightly sensitive to penicillin and sensitive to chlortetracycline, oxytetracycline, tetracycline, streptomycin, chloramphenicol, and erythromycin. In view of the favourable response of the patient to treatment, penicillin and novobiocin were continued. On the fifth day of treatment, low-grade fever returned and the heart murmur was becoming more harsh. Novobiocin was increased to

3 g. daily, probenecid in a dose of 7½ grains four times a day was added to sustain the blood penicillin levels, and penicillin was increased to a total of 18 million units daily as aqueous penicillin in divided dosage. On the eighth day of treatment, a fine polyethylene tube was inserted into the forearm and a rubber-covered adapter attached; two million units of aqueous penicillin was given by this means intravenously every two hours. Novobiocin was decreased to 500 mg. six hourly because of the development of nausea.

On the 10th day of therapy, October 5, 1956, the patient's temperature was spiking to 104° F. and she appeared quite ill. Penicillin and novobiocin were discontinued and chloramphenicol 1 g. eight hourly i.m. was commenced. On the following day, a further positive culture for staphylococcus was obtained. As fever continued, erythromycin 1 g. i.v. eight hourly was added. After two days of this treatment, the temperature subsided to 100° F., and once again the patient improved. Examination of the heart still revealed a rough systolic apical murmur, grade 3 in intensity, and many petechiæ were in evidence. After three days of combined chloramphenicol-erythromycin therapy the chloramphenicol was switched to the oral route in the same daily dosage—500 mg. four hourly. Erythromycin was continued intravenously 1 g. eight hourly. On the sixth day of chloramphenicol and erythromycin treatment the chloramphenicol was reduced to 2 g. daily in divided dosage, and erythromycin was now given by mouth—750 mg. six hourly. However, after four days of the use of oral antibiotics the patient again became febrile and ill, with temperature to 104° F.; accordingly, the parenteral route was resumed again, each antibiotic being given in the dosage of 1 g. three times daily.

A futher positive blood culture was obtained on October 24. The patient remained ill, and on October 30 she was given a combination of erythromycin 1 g. eight hourly i.v., penicillin 12 million units in divided dosage (i.m. and i.v.), and bacitracin 20,000 units i.m. six hourly. On November 1, acute cardiac failure supervened, with the occurrence of pulmonary œdema. The patient responded well to digitalization, but her hyperpyrexia continued and she appeared critically ill, with fever, chills, anorexia and the general behaviour seen with severe toxæmia. On November 2, penicillin, erythromycin, and bacitracin were all discontinued, and tetracycline (2 parts)-oleandomycin (1 part) commenced in the dosage of 500 mg. four hourly by mouth. On November 3, the temperature ranged between 99° F. and 101° F.—a distinct improvement. On November 4, the temperature rose to 101° F. and on November 5, it ranged between 98.6° F. and 100° F. She appeared much improved. Between November 7 and November 13, the temperature ranged between 98° F. and 99.6° F. and from this time on remained normal. In all, the patient received the tetracycline-oleandomycin preparation in the same dosage—that is, 500 mg. four hourly, or 3 g. daily for 74 days, the drug being continued until January 14, when a total of 222 g. had been used. This large and prolonged dosage was followed because of the previous relapses, and it was also felt desirable to carry on with the antibiotics until the patient had passed through a menstrual period without relapse—which she did in the first week of January. Blood cultures were negative on December 19, 20 and 21, and on January 16 and 18, 1957. An infection with *Monilia albicans* in the oral cavity and about the genitalia appeared during the oral use of chloramphenicol and erythromycin. It disappeared within a few days of treatment with nystatin, 500,000 units t.i.d., and the monilial infection did not appear again, nystatin 500,000 units b.i.d. being used throughout the remainder of the time the patient was on antibiotic therapy, including the time she received tetracycline-oleandomycin.

At no time during treatment with tetracycline-oleandomycin did the patient experience any nausea or bowel upset. On January 11, 1957, blood examination revealed a red cell count of 5,200,000, Hb. value 15.0 g. %, white cell count 7300 with a normal differential count. After discontinuance of the antibiotics, the patient was kept under observation until January 30, during which time three negative blood cultures were obtained. She was discharged on January 30. When last seen, on April 23, 1957, her heart still manifested a rough systolic murmur at the apex, grade 2-3 in intensity. As a trial without digitalis had resulted in tachycardia, it had been resumed, but there was no other manifestation of heart disease. She was able to do her housework.

Unfortunately we did not have available the means of testing the *in vitro* bacterial sensitivity to the tetracycline-oleandomycin used. We cannot say how tetracycline or oleandomycin alone would have worked out. However, the case does illustrate the fact that large amounts of the antibiotic combination were tolerated over an extended period of time, and that their use proved lifesaving in a condition associated with a high mortality rate.

306 Royal Trust Bldg.

PANCREATITIS, A DIAGNOSTIC CLUE TO HYPERPARATHYROIDISM

Hyperparathyroidism has been discovered in the investigation of bone cysts, urinary tract calculi and peptic ulceration. It is suggested that pancreatitis may also be related. Two cases of concomitant parathyroid tumour and pancreatitis are presented and others cited from the literature. Serum calcium levels under these circumstances vary so that the evaluation of both diseases is rendered difficult, for the hypercalcæmia may be reduced to deceptively normal levels by the pancreatitis. It seems likely that pancreatitis may be a complication of hyperthyroidism and may, therefore, be a diagnostic signpost to overactivity of the parathyroid glands.—O. Cope *et al.*: *Ann. Surg.*, 145: 857, 1957.

CATECHOL AMINES IN BLOOD, URINE, AND TUMOUR IN A PATIENT WITH PHÆOCHROMOCYTOMA

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EARLY and accurate diagnosis of phæochromocytoma in patients presenting with hypertension has been facilitated by the recent development of chemical methods for the estimation of adrenaline and noradrenaline in urine (Goldenberg *et al.*, 1954,[1] von Euler *et al.*, 1957[2]). From a normal combined urinary excretion of less than 100 μg., values may increase up to 3000 μg. daily; in most instances the increase is predominantly in noradrenaline.

Although similar attempts have been made to estimate circulating blood levels of adrenaline and noradrenaline in these and other patients in whom high levels might be expected, inadequate sensitivity and specificity of the available methods have limited the value of data obtained.

TABLE I.—URINARY EXCRETION OF CATECHOL AMINES (μG. FREE BASE PER 24 HOURS)

	Days	*Adrenaline*	*Noradrenaline*
Preoperative.....	7 - 8	309.0	228.6
	2 - 3	157.6	121.7
Postoperative.....	2 - 3	0.8	28.8
	4 - 5	0.7	31.1
	5 - 6	1.1	18.1
	17 - 18	0.2	25.8

Plasma and urine samples, together with a tumour extract, obtained from a patient showing the classical features of phæochromocytoma, have been analyzed. The results are presented here.

The fluorimetric method employed for the estimations was modified from that described by von Euler and Floding.[3] It involves separation of adrenaline and noradrenaline by means of separate filters after oxidation at pH 6. For blood samples the accuracy of the method appears to be limited to estimations of plasma levels of adrenaline and noradrenaline above 0.5 μg. per litre.

Preoperative urine samples from this 46-year-old female patient showed an increased content of adrenaline and noradrenaline (Table I). Postoperatively the values were normal.

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Data obtained by estimation of the adrenaline and noradrenaline content of peripheral venous plasma before and after surgical removal of the tumour are shown in Table II. Several features are of interest. Firstly, the close correlation between the adrenaline-noradrenaline ratio (1.8) in peripheral venous plasma (withdrawn during surgical manipulation of the large tumour) and the ratio (1.7) found by estimation of the catechol amine content of the tumour (adrenaline 1.9 μg.; noradrenaline 1.1 μg. free base/g). Secondly, an unusual finding is the high proportion of adrenaline found in samples of blood and urine before tumour removal, and in the tumour itself. Also of note are the extremely high blood levels of both amines during surgical manipulation.

TABLE II.—CATECHOL AMINES IN PERIPHERAL VENOUS PLASMA (μG. FREE BASE PER LITRE)

	Adrenaline	*Noradrenaline*
Before anæsthesia.....	2.9	2.7
Patient anæsthetized, before operation.....	5.6	6.5
During surgical manipulation.....	170.4	95.1
18th postoperative day.....	0.2	0.3

This case clearly re-emphasizes the diagnostic value of urinary catechol amine determination in these patients. It appears also that useful confirmation might be obtainable in similar cases by estimation of adrenaline and noradrenaline in peripheral venous blood.

The authors are indebted to Drs. E. Goldstein and C. Schneiderman, The Jewish General Hospital, Montreal, for permission to publish details of this case.

REFERENCES

1. GOLDENBERG, M. *et al.*: *Am. J. Med.*, **16**: 310, 1954.
2. VON EULER, U. S. AND STRÖM, G.: *Circulation*, **15**: 5, 1957.
3. VON EULER, U. S. AND FLODING, I.: *Acta physiol. scandinav.*, **33**: (suppl. 118), 45, 1955.

STROPHANTHIN THERAPY IN ATRIAL FLUTTER

The effect of intravenous strophanthin therapy in 18 patients with 22 attacks of atrial flutter was studied by Scherf *et al.* (*Am. J. M. Sc.*, 234: 180, 1957). Conversion of atrial flutter to atrial fibrillation occurred in eight attacks and to normal sinus rhythm in six others. Six patients did not respond to therapy. Four of these died within a few weeks from their underlying noncardiac disease. One patient showed only an increase of the atrioventricular block from 2:1 to 4:1. There was only one instance of nausea and vomiting and no instance of ectopic rhythm. Strophanthin is recommended for the conversion of atrial flutter into fibrillation or sinus rhythm.

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STANDARDS OF HOSPITAL CARE

In May, our President Dr. Morley Young presented some thoughts on the maintenance of a high standard of hospital care to the Western Canada Institute for Hospital Administrators and Trustees. This paper has now been published in *Canadian Hospital Journal* (Sept. 15, 1957), and is worthy of consideration by all those concerned with hospitals. Dr. Young pointed out that good medical care in hospitals was not a static concept but a dynamic and ever-changing thing. To maintain the highest standard of care two things are necessary—eternal vigilance on the part of hospital personnel and a realization of the issues involved by all those who use the hospital whether administrators, medical and nursing personnel, patients or the general public.

Dr. Young shows that certain changes in our society which might superficially be regarded as blessings are, like most blessings, by no means unmixed. Government aid that has made possible a high standard of equipment and financing may possibly have brought with it a lack of appreciation on the part of the patient and the personnel of the good things they have thus obtained. It is possible that there is a tendency to rely on the equipment to give care, rather than the individual, and for individuals to become dedicated to a salary rather than a task.

The advent of the 40-hour week has been hailed as a social advance, but it is only one if the remaining 128 hours can be wisely used. It has created problems in hospital operation, for neither obstetric nor surgical emergencies are arranged on a 40-hour-week basis.

It is scarcely necessary to elaborate on the drawbacks of the antibiotic age. The advent of the resistant staphylococcus is a thorn in the flesh of hospital authorities throughout the world and it has even been suggested that many hospitals may now be more dangerous to the patients than those of the pre-Lister era. The use of antibiotics thus implies a simultaneous meticulous attention to aseptic techniques.

Early ambulation after operation or delivery has changed the nursing picture. Since patients no longer lie in bed for days on end, attention to details of nursing care may be less strict than it should be. As regards medical care, the growth of specialism has also robbed the patient of something, for the resultant dilution and division of responsibility will not be to his benefit unless there is proper co-operation and co-ordination of effort among the medical staff.

Prepayment insurance schemes have very obvious benefits, but they also have the associated unpleasant tendency for subscribers to demand unnecessary hospital service and block hospital beds to the detriment of the community.

In his address, Dr. Young examines the responsibility of hospital administrators, medical and nursing personnel, the patient and the public in maintaining standards. He warns us that "high standards of medical care" does not mean "highly standardized medical care". He also emphasizes that whereas the governing body of a hospital is under an obligation to the community to maintain a high standard of medical care, this body has a right in its turn to expect that the community will interest itself and co-operate in supporting hospitals. Speaking of the relationship between the governing body and the professional staff, Dr. Young gives it as his opinion that there should be an approved method of guiding boards in the appointment of medical staff. He also feels that in any hospital large enough to have three staff members some organization and division of duties is necessary. Regulations will have to be established, staff meetings arranged, and records kept at the most efficient minimum.

Dr. Young pleads for a realistic approach to the problem of supplying adequate nursing care. We must say quite firmly to ourselves that 75-80% of the young women we train for nursing will be lost shortly after training by reason of marriage. Hence plans for nursing recruitment and training must be considered in the light of

the 75 who go rather than the 25 who remain in career nursing.

Dr. Young ends by stressing the need for constant education of the public on aspects of good medical care. Members of the public should know what accreditation of hospitals means to them; they should realize the benefits to them of a properly organized medical staff, of record-keeping and of hospital rules and regulations. Thus the maintenance of high standards of medical care in hospitals is seen to be a co-operative effort in which every member of the community has a part to play.

INFLUENZA

The influenza virus has again asserted itself in the recent epidemic in Asia. The virus was first isolated in 1933, and three types A, B and C have now been identified. Within each type, numerous strains differing from each other in their antigenic structure can be distinguished. All the major epidemics in recent years have been associated with type A virus. Types B and C have been encountered chiefly in localized outbreaks. It appears that the influenza virus type A is constantly undergoing antigenic change. These new mutant strains differ substantially from those encountered in previous years. Immunity to one strain will not protect against a new strain; thus when a suitable mutant arises it will encounter a relatively non-immune population.[1] The causative organism in the 1957 Asian epidemic is a new mutant strain belonging to type A influenza.

The epidemic appears to have started in China in the early months of this year. In April, reports came from Hong Kong of a severe outbreak, mainly among refugees. The disease spread rapidly, involving a large proportion of the population, but was very mild in nature and no deaths were reported initially.[2] Singapore was soon involved and by May it had spread to Japan, India and Siam.[3] As the incidence abated in Asia, outbreaks were reported in Australia and Africa. The virus has been introduced into Europe, particularly Holland, and to North America. So far there is no evidence of epidemic spread in these latter countries but small outbreaks may act as a "seeding" of the population which is known to occur prior to a major epidemic. Spread of infection seems to be determined more by mass contact than by age or race;[4] thus ocean travellers constitute a greater threat than air passengers.

The disease continues to be of a very mild nature with fever of 102-103° F. lasting 48-96 hours. Muscular pains, lassitude and severe headaches are the chief symptoms.[5] The mortality rate continues at a low level.

It is assumed that the epidemic will strike the northern hemisphere within the next few weeks, but there is no reason to fear that it will increase in virulence. Careful watch should be kept for a tendency to increased mortality among young adults, which was characteristic of the pandemic of 1918-19.

Since first isolated in 1933, the influenza virus has been extensively studied. After the Second World War, the newly formed World Health Organization established an Influenza Centre in London to study and compare strains isolated in different countries with a view to establishing a better understanding of epidemics and in the hope of developing a vaccine. Experience showed that for a vaccine to be effective, it was necessary to incorporate the prevailing epidemic strain.

Strains isolated in Asia, Europe and America this year have been studied in London and Washington. They have been identified as belonging to influenza type A. While they are closely related to each other, they bear no relationship to any previously isolated A strain.[6] Thus a vaccine prepared against existing strains would not be effective against this new mutant. Laboratories in Europe, North America and Australia are now preparing a vaccine incorporating this new strain. It is reasonable to expect that the vaccine will afford considerable protection if administered prior to the ensuing epidemic. It is unlikely that another mutation will occur in a short space of time. Production of sufficient vaccine to protect the entire population at risk will not be possible in the time available. Thus supplies should be reserved for special groups. Medical and other essential services should receive priority, while the aged and those chronically ill should be considered.

There is no specific treatment for influenza, but patients should be advised to remain in bed at the first sign of illness. This will not only help to lessen the severity of the attack but will also assist in isolating the case. Antibiotics should be withheld in readiness to combat secondary

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complications. With the wide-spectrum antibiotics available today, it is unlikely that we shall experience a repeat of the high mortality figures of the pandemic of 1918-19 in which secondary invaders played a major role.

Studies of influenza epidemics have led to two theories of the method of spread of the virus. One is that mutations arose simultaneously in widely separated areas, assuming that the mutations were in a similar direction. The other theory held that a single suitable mutation occurred followed by rapid spread.[1] The present experiences favour the latter theory. M.C.

REFERENCES

1. ISAACS, A.: *Lancet*, 2: 960, 1956.
2. WHO Weekly Epidemiological Report, No. 19, May 10, 1957.
3. *Lancet*, 1: 1182, 1957.
4. *Ibid.*, 2: 233, 1957.
5. *Ibid.*, 2: 93, 1957.
6. WHO Weekly Epidemiological Report, No. 23, June 7, 1957.

Editorial Comments

HÆMOLYTIC DISEASE OF THE NEWBORN

It is ten years since the treatment of hæmolytic disease of the newborn by exchange transfusion, using the umbilical vein, was first practised.[1] Though the advantages of an exchange over a simple transfusion were initially in doubt, the work of Allen[2] in Boston and of Mollison and Walker[3] in England converted the hesitant, and exchange transfusions are now carried out on a wide scale on selected cases of hæmolytic disease. The generally recognized indications for this procedure are a positive direct Coombs test with a cord hæmoglobin below 14.8 g. %, prematurity, a history of a severely affected sibling, or the rapid onset of jaundice. The result of treatment on the above lines should ensure that more than 95% of infants born alive survive, whereas with simple transfusions the survival rate is only 80%. This reduction in mortality should be mirrored by the Registrar General's returns, and the latter were therefore recently examined in England by Walker and Mollison.[5] They found that the mortality had only fallen from 0.8 to 0.6 per 1000 live births and not to the anticipated 0.2 per 1000 live births. To find out why so many more infants had died of hæmolytic disease than expected, they reviewed in detail all the deaths in 1953 and 1955 reputedly due to hæmolytic disease. Briefly, their findings were in part reassuring and in part disturbing. Many cases of hydrops fetalis and kernicterus had been ascribed incorrectly to hæmolytic disease; in fact, 24% of the cases of hydrops and 33% of the cases of kernicterus occurred in the absence of hæmolytic disease, these cases of kernicterus were associated with prematurity and the high number found with this condition was perhaps surprising. The number of deaths due to hæmolytic disease was therefore less than the returns suggested, but they were still disappointingly high. There were several reasons for this. With regard to antenatal care, the obstetricians' responsibility, 30% of the mothers had not had routine antenatal Rh testing; in some instances, but not in all, this may have been because the mother did not attend for antenatal supervision, and in 30% of cases the mother had been delivered at home and not in hospital where adequate facilities for treating the affected child were available. Analysis showed that nearly 20% of the deaths were due to failure to predict the disease in the infant. With regard to postnatal care, the Coombs test was done on only 78% of cases (1955) and the cord hæmoglobin estimated in only 65% (1955), and the significance of early jaundice was missed in 10%. All the cases under discussion were severe, for all the infants had died. All should have been given the benefit of an exchange transfusion and yet only 58% were; 29% had had no transfusions at all. Of the 321 infants who had been given an exchange transfusion, the pædiatricians' responsibility, the exchange either failed or was inadequate in 121. The definition of an adequate exchange given by Walker and Mollison is 40 ml. per lb. body weight; this is conservative, for Walker[4] has recommended a minimum of 60 ml. and has advised 80 ml. should the baby's condition warrant it; the exchange should be repeated if the indirect serum bilirubin threatens to rise above 20 mg. %. It is interesting to note that whereas in 1953, 105 infants had died of kernicterus and only 28 as a result of the exchange, in 1955 the mortality from kernicterus had fallen to 82, but that from the exchange had risen to 60. It might be expected that with more experience the mortality from the exchange should have fallen, but this was not so; it would appear that more pædiatricians were carrying out exchange transfusions in 1955, and that many of these lacked experience. In the two years the total death rate from kernicterus and from exchange transfusions combined had actually risen by 5%.

It would be unwise to infer that what has happened in the United Kingdom happens in Canada, because medical practice in the two countries is very different—in Canada, for example, a higher proportion of mothers are delivered in hospital; but the studies of Walker and Mollison do indicate that there is often a wide gap between ideal and actual treatment, and a simple analysis of the returns for Canada would probably indicate whether the results of treatment in this country are as satisfactory as might be wished.

REFERENCES

1. DIAMOND, L. K.: *Proc. Roy. Soc. Med.*, 40: 456, 1947.
2. ALLEN, F. H., JR., DIAMOND, L. K. AND VAUGHAN, V. C.: *Am. J. Dis. Child.*, 80: 779, 1950.
3. MOLLISON, P. L. AND WALKER, W.: *Lancet*, 1: 429, 1952.
4. WALKER, W. AND NELIGAN, G. A.: *Brit. M. J.*, 1: 681, 1955.
5. WALKER, W. AND MOLLISON, P. L.: *Lancet*, 1: 1309, 1957.

SUDDEN LOSS OF MEMORY

Sudden loss of memory is probably commoner in fiction than in real life, but Kennedy and Neville,* two British psychiatrists, were able to collect 74 patients and study the causative factors. They were particularly interested in assessing the relative incidence of organic, psychoneurotic and volitional factors in such cases. Usually, the first thing to do is to exclude fraud in many of these cases; the absentminded cashier who absconds with the cashbox is not likely to be suffering from organic disease. However, in the present series 27 out of the 74 patients were found to have some organic nervous disease; the types of disease encountered included idiopathic epilepsy, head injury, chronic encephalitis lethargica, disseminated sclerosis, presenile dementia, cerebral syphilis, and other encephalopathies. In 35 cases there was a hysterical amnesia without organic disease, and in 22 of these there had been a previous history of hysteria. Fifteen persons were of psychopathic personality or had a very bad employment record, while two were feebleminded or illiterate. Only five would admit to malingering. In six cases the fugue was associated with an attempted suicide, and in five cases a depressive state was found. It is noteworthy that only two of the patients were senile and only three under the age of 12.

The authors are careful to point out that the organic disease *per se* was not responsible for loss of memory, but appeared to pave the way to a hysterical reaction or to lower the threshold at which stress became intolerable. Even in the presence of gross organic disease, a complete and convincing psychogenic cause could often be found. Thus in the majority of cases the amnesia was shown to be a psychological escape mechanism, designed to protect the individual from intolerable mental pain or tension.

Amnesia of a functional type rarely persists longer than a few hours or days. Either the patient recovers his memory or some other condition supervenes, such as a hysterical disability. With a good previous personality, the prognosis is usually very good. Malingering amnesia is not usually difficult to detect, but a hysterical amnesia may often be mistaken for malingering, and indeed the hysteric may confess to malingering when he is actually suffering from an organic or functional disorder.

Because recovery is the rule, the method of treatment of a sudden loss of memory is not important. Three equally good methods are: hypnosis, suggestion during injection of an intravenous barbiturate, and therapeutic anamnesis by encouraging the patient to extend his history until he realizes his ability to recall details normally. Finally it is noted that, if tension is sufficent, anybody may develop an amnesia although organically vulnerable and psychopathic individuals have a lower threshold.

*Brit. M. J., 2: 428, 1957.

CIVIL DEFENCE DAY

The public reaction to the words "civil defence" falls roughly into three categories. First of all there are the people who have decided that civil defence against atomic war is impossible and futile. This fatalistic attitude makes a good excuse for doing nothing and overlooks the real concept of civil defence. Secondly, there are the citizens who are just not interested, or for a variety of reasons find it best to forget all about the subject. Thirdly, there is the minority of citizens who have appreciated that civil defence does not mean only attempts to minimize disaster after atomic or hydrogen bomb attacks, but means the general organization of each community to deal with disasters of any kind.

The office of the Federal Civil Defence Coordinator has officially announced that Friday, October 4, 1957, will be National Civil Defence Day. The object is not to undertake extensive exercises and demonstrations on that day but to focus the attention of every Canadian citizen on the concept of civil defence. An efficient civil defence organization can work wonders in time of fire, flood, earthquake, tornado, explosion or other catastrophe. This has already been demonstrated on this continent. Such an organization is the responsibility of every citizen, and since one of the essential services included in civil defence is the health service for the treatment of injuries and maintenance of community health, the medical profession are particularly requested to interest themselves in their local civil defence organization. Physicians should learn what civil defence can do for them and their community, and then find out what they can do for civil defence. Help in organizing a local civil defence organization and offers to serve in it will always be welcome. In addition, it might be timely to refer once again to the articles contained in our special Civil Defence issue published on March 1, 1957.

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Medical News in brief

INTRAMUSCULAR IRON FOR IRON-DEFICIENCY ANÆMIA

In 1954 a drug preparation suitable for intramuscular administration of iron was developed in Britain and reported on in *Lancet*. Now comes confirmation from the Mayo Clinic of the efficacy of this compound in the treatment of iron-deficiency anæmia. Hagedorn (*J. A. M. A.*, 164: 1642, 1957) administered the product Imferon to 10 patients with hypochromic anæmias, mostly caused by a persistent gastro-intestinal bleeding. The preparation was found free from any local or general toxic reactions, and patients preferred intramuscular to intravenous administration. Hæmatological response was satisfactory, and it is suggested that when parenteral administration of iron is desirable, the intramuscular product be used in preference to an intravenous one.

ERRONEOUS BLOOD ALCOHOL FINDINGS AT AUTOPSY

Turkel and Gifford of San Francisco (*J.A.M.A.*, 164: 1077, 1957) have been studying coroners' cases in which the question of consumption of alcohol before sudden death arose. They have noted that alcohol diffuses out of the intact stomach post mortem; therefore blood samples taken from the region of the heart may show a falsely elevated alcohol level. This might lead to the erroneous belief that the deceased was in a state of drunken stupor at the moment of death. They now record the results of blood sampling from 75 autopsies. In 24 cases no alcohol was found in either the femoral vein blood or the blood pooled in the pericardial sac, suggesting that alcohol is not produced post mortem in the cadaver. In 51 cases alcohol was found in the blood. In 35 of these the cardiac blood had a much higher alcohol content than the femoral blood. A deceased person might be pronounced drunk on the evidence of a sample taken from the pericardial sac, and the authors recommend that in medico-legal work post-mortem samples of blood for alcohol analysis should be taken from the femoral veins.

EXTRACORPOREAL CIRCULATION IN CARDIAC SURGERY

A group from the surgical centre Marie-Lannelongue, Paris, France, report the first use in France of an extracorporeal circulation in cardiac surgery (*Bull. Acad. nat. méd.*, 141: 437, 1957). They have employed the system of Lillehei and de Wall. In their report to the Academy of Medicine they mention a series of 18 cases operated upon with seven deaths. Of the first 10 patients operated upon six died, but they point out that patients in the worst condition were chosen. Their first cases included three of interventricular septal defect, three of pulmonary stenosis and three of pulmonary infundibulum stenosis. Studies have also been carried out on animals to determine the scope and limits of induced cardiac arrest. Results were so encouraging that the authors have now operated upon one case of tetralogy of Fallot and one of interventricular septal defect with success.

TREATMENT OF HYPERTHYROIDISM IN PREGNANCY

The risk of treatment of hyperthyroidism with antithyroid drugs in pregnancy has been variably assessed. Bohm and Imholz (*Deutsche. med. Wchnschr.*, 82: 846, 1957) discuss the pros and cons of the use of these drugs in the light of their experience in one case. This woman was eight months pregnant when a severe thyrotoxicosis appeared after a febrile infection; the thyroid condition failed to respond to either x-irradiation or sedation. It was, however, controlled with 1-methyl-2-mercaptoimidazole (methimazone) in doses of 20 mg. three times a day to a total of 3.18 g. At term a hypothyroid child was delivered, but within 10 days there was a spontaneous regression of all signs of hypothyroidism.

Antithyroid drug treatment of hyperthyroid pregnant women should if possible be started only in the second half of pregnancy, and then with minimal doses, continuing as long as is absolutely necessary. In the first half of pregnancy, a subtotal thyroidectomy is preferred. Antithyroid drugs must not be given during breast feeding.

RESECTION AND HOMOGRAFTING OF INNOMINATE AND CAROTID ARTERIES

When either the innominate or the carotid arteries are involved in aneurysm, tumour, arteriovenous fistula or arteriosclerotic occlusion, a special problem is presented which does not arise in surgical treatment of other arteries of this size. If they are to be treated by excision of the affected segment and replacement by a homograft, arrest of the circulation to the brain during the procedure may cause ischæmic damage to the latter. De Bakey and Crawford of Houston, Texas, (*Surg. Gynec. & Obst.*, 105: 129, 1957) describe the successful resection of an aneurysm affecting the right common carotid and the innominate arteries and its replacement by a bifurcation homograft. During the operation, a by-pass made of tygon tubing and two lucite cannulas was employed. This was inserted into the innominate below the resected segment and into the common carotid above the site of resection and served as a shunt during the operation.

(Continued on advertising page 50)

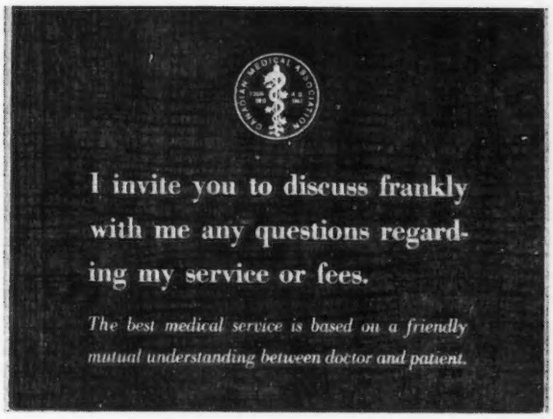
PUBLIC RELATIONS FORUM

Conducted by L. W. HOLMES,
Assistant Secretary, C.M.A.

PR AID FOR DOCTORS' OFFICES

PROBABLY the greatest threat to good medical public relations is misunderstanding. The patient who receives medical treatment without understanding what it is or why he receives it, or the one who receives an unexpectedly large perhaps undetailed bill, is a potential source of complaints about the profession.

The solution is prevention of misunderstanding by enlightenment. Let the doctor explain his treatment and why he prescribes a certain course of action.



More important, let him discuss his fees with the patient, preferably in advance. By attempting to estimate his own bill and, if possible, anticipating hospital and drug costs, the doctor can eliminate many damaging complaints.

Unfortunately, too often the doctor is loath to introduce discussion of fees.

Realizing this—and aware that mutual understanding between doctor and patient is essential to good medical service and good public relations—the Canadian Medical Association's Committee on Public Relations has authorized production of a plaque for use in the doctor's office inviting patients "to discuss frankly . . . any questions regarding service or fees".

The plaque—English and French versions of which are illustrated—measures 9″ by 6¾″. Wording in gold is printed on walnut finish paper fused to heavy ⅛″ board. Edges of the plaque are bevelled and gilded. An easel mounted on the back permits standing the plaque on the desk, or hanging it on the wall.

The plaques are now ready for distribution and one free copy in English *or* French will be sent on request. Additional copies will be available at a charge of 75 cents each.

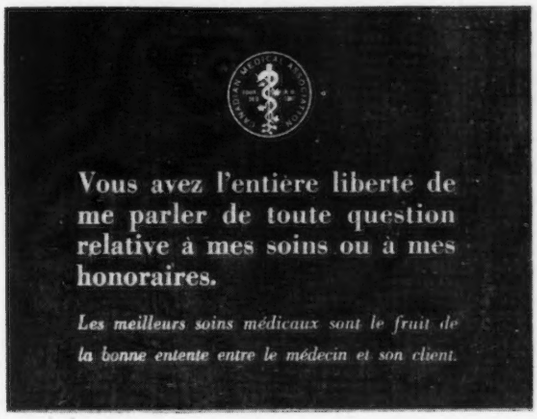
Requests for plaques should be sent to Mr. L. W. Holmes, Assistant Secretary, The Canadian Medical Association, 150 St. George Street, Toronto 5, Ontario.

POUR LE MEDECIN

LA PLUS grande menace aux bonnes relations entre le médecin et ses clients vient probablement de l'incompréhension. Le patient qui reçoit un traitement et qui n'en sait ni la raison ni la cause, ou celui qui reçoit une note assez élevée et non-détaillée peut se plaindre de la profession médicale.

La solution de ce problème est fondée sur la prévention de cette incompréhension. Que le docteur explique le traitement donné au patient et qu'il lui montre le pourquoi de telle ou telle prescription . . . etc.

Il doit discuter ses honoraires avec le patient, préférablement à l'avance. De plus, en tentant d'estimer sa note et, si possible d'évaluer par anticipation les frais d'hôpital et des produits



pharmaceutiques, le médecin peut éliminer beaucoup de critiques de la part des patients.

Il est déplorable que, trop souvent, le médecin n'aime pas à discuter ses honoraires.

Se rendant compte de cet état de chose, et sachant qu'une bonne entente entre le médecin et son client est essentielle à de bons soins médicaux, le comité des relations extérieures de l'Association Médicale Canadienne a autorisé la production d'une plaque assurant les patients qu'ils ont "l'entière liberté de me parler de toute question relative à mes soins ou à mes honoraires".

Cette plaque mesure 9″ x 6¾″. Le lettrage doré est imprimé sur du papier à l'imitation de chêne et apposé sur une planchette de ⅛″. Les bords de la plaque sont biseautés et dorés. Un support monté à l'arrière permet de poser la plaque sur un bureau ou de la suspendre au mur.

Ces plaques sont maintenant prêtes à être distribuées et un exemplaire gratuit, en anglais ou en français, vous sera envoyé sur demande. Des copies supplémentaires peuvent être obtenues au coût de 75c chacune.

Les demandes doivent être adressées à M. L. W. Holmes, secrétaire-adjoint, l'Association Médicale Canadienne, 150 St. George Street, Toronto 5, Ontario.

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MEDICAL FILMS

CONTINUING the listing of available films on medical and related subjects, we list below additional films in the field of anæsthesiology. These films are held in the National Medical and Biological Film Library and are distributed by the Canadian Film Institute, 142 Sparks Street, Ottawa, Ontario. Evaluations, where given are those submitted by the distributor.

Relief of Pain in Childbirth (1953) Sound Colour 18 minutes.

Produced for Imperial Chemical Industries Limited. Made in collaboration with the Department of Gynæcology and Obstetrics, Guy's Hospital, London.

Description.—The film portrays one method of obstetrical analgesia widely used in the United Kingdom—namely N_2O and air or Trilene and air, self-administered. Opens by defining an ideal analgesic agent for obstetrical use, and then proceeds to a description of the two inhalational methods. The properties of nitrous oxide are described and the methods of use of the gas. The auto-administration by the patient is shown; apparatus such as Minnitt's is described using animated diagrams; Chassar Moir's and Elam's equipment is also mentioned. Trilene is described, and its administration. The film closes by stressing the importance of proper instruction in the use of the inhalers in advance of the time of need.

Appraisal (1954).—Obviously made for U.K. consumption (doctors, midwives, nurses, medical students—even patients). Most of the equipment demonstrated is not available in Canada, nor is this method of pain relief in common use in Canadian hospitals. Subject is treated in a somewhat elementary manner, as befits the emphasis on self-administration. With these reservations, it is a well-made, effective and interesting presentation for any interested professional audience of doctors, nurses, or medical students. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($3.00). For purchase apply to Publicity Department, Imperial Chemical (Pharmaceuticals) Limited, Fulshaw Hall, Wilmslow, Manchester, England.

Respiratory and Cardiac Arrest (1945) Sound B & W 15 minutes.

Produced by Realist Film Unit, for Imperial Chemical Industries Limited. Technical Advisers: Department of Anæsthetics, Westminster Hospital, London. *The Technique of Anæsthesia series, No. 9.*

Description.—An instructional-training film, illustrating the management of respiratory and cardiac arrest during anæsthesia. Causes are discussed and apparatus which should be on hand is indicated. For respiratory arrest, methods of artificial respiration are demonstrated, including treatment of respiratory obstruction. Signs of cardiac arrest are discussed, and treatment as follows: forced oxygen; heart puncture; indirect heart massage, direct heart massage; injection of adrenaline and massage continued; postoperative treatment.

Appraisal (1946).—A good—and unique—presentation of a subject most difficult to portray in film. Recommended for senior medical students, interns, general surgeons and practitioners, and specialists in anæsthesia. Perhaps does not give a true sense of the critical emergency of such situations—everyone moves too slowly and nonchalantly, and film leaves too secure a feeling that if these steps are followed all will end happily. Cardiac arrest scenes faked, but film recommended nonetheless. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($1.50). Purchase (in Canada) from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.Q.

The Role of Carbon Dioxide in Convulsions During Anæsthesia (1942) Silent B & W 10 minutes.

Produced by the Departments of Anæsthesia, Radiology and Photography, University of Wisconsin Medical School, Madison, Wisconsin.

Description.—An instructional-record film, demonstrating the author's theory as to one cause of convulsions during anæsthesia; how excess CO_2 in inspired atmosphere may cause muscular activity which may progress to generalized convulsion. Demonstration shows, in nitrous oxide-oxygen anæsthesia, how character of respiration changes as inhaled atmosphere changes from 85% nitrous oxide, 15% oxygen to 30% CO_2, 70% oxygen. Beginning motor stimulation evidenced in muscular activity of forehead, eyelids and cheeks, and its progress to all skeletal muscles—convulsion; disappearance of hyperactivity when atmosphere changes to 100% oxygen for two breaths and then to original nitrous oxide-oxygen mixture. Danger of excess CO_2 in treatment of respiratory depression during anæsthesia caused by barbiturate or opium premedication.

Appraisal (1945).—A most unusual film, illustrating in a unique way the harmful effects of carbon dioxide under certain circumstances. Subtitles and explanatory matter lengthy but necessary; visual portion impressive and convincing. Author's theory rapidly being accepted. Recommended for senior medical students, general practitioners, interns and specialists in anæsthesia. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($1.50). For purchase apply to American Medical Association, 535 North Dearborn Street, Chicago, Illinois.

Open Drop Ether (1944) Sound B & W 31 minutes.

Produced by Realist Film Unit, for Imperial Chemical Industries Limited. Technical Advisers: Department of Anæsthetics, Westminster Hospital, London, England. *The Technique of Anæsthesia series, No. 2.*

Description.—An instructional-training film, demonstrating the principles and practice of ether anæsthesia by the open drop method. Essential apparatus and premedication are discussed, and the film then demonstrates the technique of administration (the four stages of anæsthesia described and illustrated), with procedure for administration and checking patient's reactions shown in detail. Pitfalls of ether anæsthesia discussed. Corrective and preventive procedures shown for the following: handling of the conscious patient during 1st stage; struggling in the 2nd stage; lack of premedication; laryngeal spasm in the 2nd stage; respiratory arrest due to overdose; laryngeal spasm due to surgical stimuli in the light anæsthesia; use of corneal reflex. Use of open drop ether in emergencies and in rural practice.

Appraisal (1945).—An excellent presentation of fundamental principles, and a satisfactory technique. The more common mistakes of the less experienced administrator are admirably shown. Good photography; commentary concise and clear. Film is eminently suitable for senior medical students, interns, general practitioners and nurses, since this method is the basis for all anæsthetic training. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($3.00). Purchase (in Canada) from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.Q.

(To be continued in our next issue)

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REVIEW ARTICLE

THE INCREASING PROBLEM OF DRUG REACTIONS*

ARTHUR R. BIRT, M.D.,† *Winnipeg, Man.*

THE PRACTICE of medicine is continually evolving. It has been aptly said that one must run to stay in the same place in medicine. With the tremendous advances in the science of medicine, particularly in the field of chemotherapy, in surgery and its ancillary services, and in public health, many diseases that were common and serious are now uncommon and easily controlled. In no branch of medicine are these changes more apparent than in dermatology and syphilology.

Skin diseases due to infestation with animal parasites are waning at the present time. DDT adequately controls pediculosis, and scabies, for some unknown reason, is becoming extremely rare. Pyogenic infections can now be relatively easily combated with many new drugs, though the problem of resistant organisms, particularly staphylococci, is becoming increasingly difficult. Public health measures have done much to control fungous infections of the skin, and the corticoids have simplified the therapy of many eczematous conditions and have given us a new approach to the treatment of the so-called collagen diseases. However, the most dramatic change has been in the field of syphilology.

It is only 50 years since Schaudinn discovered the *Spirochæta pallida*, and only a little more than 10 years since Mahoney[1] and his associates published the first report of the treatment of syphilis with penicillin. It is therefore indeed amazing that the late Dr. P. A. O'Leary,[2] an internationally recognized authority on syphilology, and the editor of the *A.M.A. Archives of Dermatology and Syphilology*, should write in an editorial in that journal in January 1955, "The diagnosis and treatment of patients with syphilis is no longer an important part of dermatologic practice." "Few dermatologists now have patients with syphilis; in fact, there are decidedly fewer patients with syphilis, and so the old label, *Syphilology*, on this publication seems no longer warranted." Since that time the journal has been known as the *Archives of Dermatology* and we have witnessed the passing of one more epoch in the kaleidoscopic picture of medicine. And yet syphilis, the great imitator, is still with us. Its very uncommonness will make it more difficult to diagnose. The alert suspicious mind that has always been required to detect syphilis will have to be keener than ever to make the diagnosis.

The lessening of emphasis on syphilis does not diminish the diagnostic problems facing us. A newer and equally competent mimic has arisen to test the diagnostic abilities of all who practise medicine. The very drugs with which we have attained some of our greatest therapeutic successes can now produce reactions that will imitate almost any known disease. Drug reactions are on the increase and have to be considered in every differential diagnosis.

A drug may be defined as any substance used in the treatment of disease. The route of exhibition may be by ingestion, inhalation, injection, or application to the skin or through the various body orifices.

The mechanisms involved in the production of drug reactions are varied and not completely understood. Rostenberg and Webster[3] suggest that the following mechanisms be considered in cutaneous reactions.

1. *Pharmacological.*—There is a predictable dose-response effect, such as the erythema produced by nicotinic acid; the argyria of silver salts; and the yellowish discoloration associated with the administration of atabrine. This group includes the primary toxic effects of overdosage and also cumulative effects.

2. *Enzymic interference.*—They consider here only the effects that are neither anticipated nor desired. The inhibition of the pyruvate oxidase system by compounds of gold, mercury and arsenic affords a metabolic explanation of the skin lesions produced by these compounds.

3. *Intolerance and idiosyncrasy.*—Intolerance is a quantitative deviation in response to a drug, such as ringing in the ears with small doses of quinine; idiosyncrasy is a qualitative deviation, as in the production of certain eruptions with iodides and bromides.

4. *Allergy.*—A specifically acquired alteration in the capacity to react, brought about by means of an antibody mechanism.

5. *Schwartzmann reaction.*—The skin site, prepared 24 or more hours previously by the injection of a toxin, reacts with a vascular purpuric or hæmorrhagic response when either the respective toxin or certain other non-related substances or toxins are injected into the blood stream.

6. *Herxheimer reaction.*—A drug causes an exacerbation of existing lesions or the development of new ones.

7. *Ecologic.*—This mechanism considers the individual in relation to his environment. An example is the effect of antibiotics destroying bacteria and letting *Monilia* grow.

8. *Biotropic.*—By this is meant the stimulating effect of the drug on other micro-organisms, such as the effect of penicillin on epidermophytosis.

Alexander[4] also considers the mechanisms involved in the production of blood dyscrasias by drugs. He emphasizes the fact that the action of a drug on the blood elements may be

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*Presidential Address, read before the Winnipeg Medical Society, May 17, 1956.

†Lecturer in Dermatology, University of Manitoba.

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quite specific. One drug may attack the granulocytes only; another the megakaryocytes; and another may wipe out all the blood elements. He believes that allergy is the mechanism that underlies the production of granulocytopenia and that immunologic factors are responsible for the production of purpura simplex and thrombocytopenic purpura. It has been demonstrated that agglutinins for platelets are formed in some of these patients, which remove the platelets, and purpura results. Aplastic anæmia, along with shock, is the most common fatal expression of drug hypersensitivity. The mechanism of its production has not been completely elucidated.

Allergy is by far the commonest method of production of drug reactions, and it is significant that even a small amount of a drug which has been well tolerated for weeks or months may suddenly produce a reaction. Considering the thousands of substances that have been used as drugs, it is indeed fortunate that relatively few account for the majority of cases of hypersensitivity. Alexander states that the drugs that cause most reactions are the sulfonamides, mercurials, penicillin, iodides, arsenicals, gold salts, barbiturates, quinacrine, the hydantoins and thiouracil.

Contrary to the concept that true allergens are complex nitrogenous substances with large molecules, simple pharmaceutical chemicals may act as specific antigens. This point was established by the brilliant work of Landsteiner[5] and his associates when they showed that simple chemical compounds may become antigenic by attaching themselves to protein.

The chemical structure of a drug may give a clue to its potential ability to sensitize. It has been shown that certain compounds, in which the benzene ring acts as a nucleus, and to which a labile amine or chlorine atom is attached, produce a high degree of antigenicity. This is particularly true if the amine is situated in the *para* position in the benzene ring. A large number of chemicals contained in foods, cosmetics, furs and dyes, as well as drugs and industrial chemicals, have this structure. As Mayer[6] has so ably demonstrated, this group has one factor in common that accounts for its increased allergenic activity. All of the chemicals in this group are readily oxidized to quinones. Quinones are highly reactive, and will unite with proteins in the body to form complete antigens. Thus, this whole group of chemicals can yield a common derivative that is able to become extremely antigenic. Because of this common characteristic it is possible for these drugs to produce cross-sensitivities.

This point can be demonstrated by the following case history. Mrs. G., white, 53 years of age, presented in April 1949 with a typical discoid lupus erythematosus on her face of three years' duration. In July 1949, a sun filter cream containing 10% para-aminobenzoic acid was prescribed. She developed an immediate acute contact type of dermatitis on her face where the cream was applied. A history taken at that time established the fact that she had had a contact-type dermatitis on her face and neck previously when she wore a black fur coat, dyed with para-phenylenediamine. In March 1950 she was seen again with an acute generalized vesicular eruption which appeared a few hours after she took one tablet of a sulfonamide for the "flu". The actual type of sulfonamide taken was not established. In August 1951 she was seen elsewhere with pruritus ani et vulvæ, and a procaine-type ointment and suppositories were prescribed. She consulted us shortly afterwards with an acute contact-type dermatitis in the affected area. Thus this patient presented with four acute eruptions within the period of a few years after exposure to para-phenylenediamine, para-aminobenzoic acid, a sulfonamide and procaine (Fig. 1). It is obvious

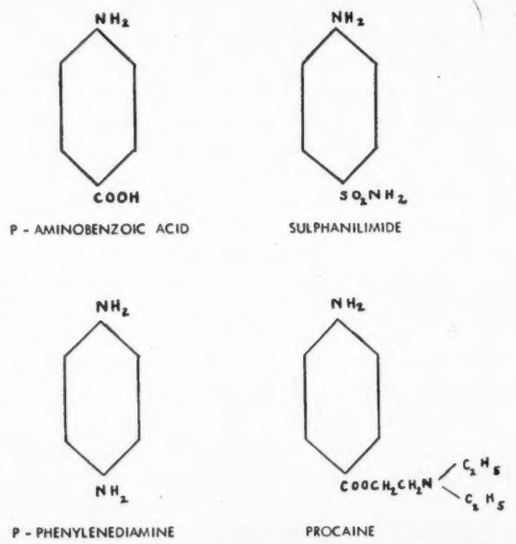

Fig. 1.—Crossed sensitivity of drugs and dyes containing a benzene ring with an amine group in the para position.

that these drugs all have a similar chemical formula with a benzene ring and an amine atom in the para position; therefore they could all be oxidized to quinones and form a common antigen. This type of crossed sensitivity may occur with several other substances having the same basic chemical structure. It can also occur between other groups of chemicals which have a common chemical denominator.

Quinones also produce granulocytopenia. Early attention to the chemical structure of chloramphenicol (Chloromycetin) when it was a new drug rightly suggested that it was potentially allergenic and possibly agranulocytopenic. It was the first discovered naturally occurring antibiotic having a benzene ring and a free nitro group in the para position.

The skin is the organ most frequently involved in drug reactions. As a rule the lesions produced are not characteristic of any one particular drug;

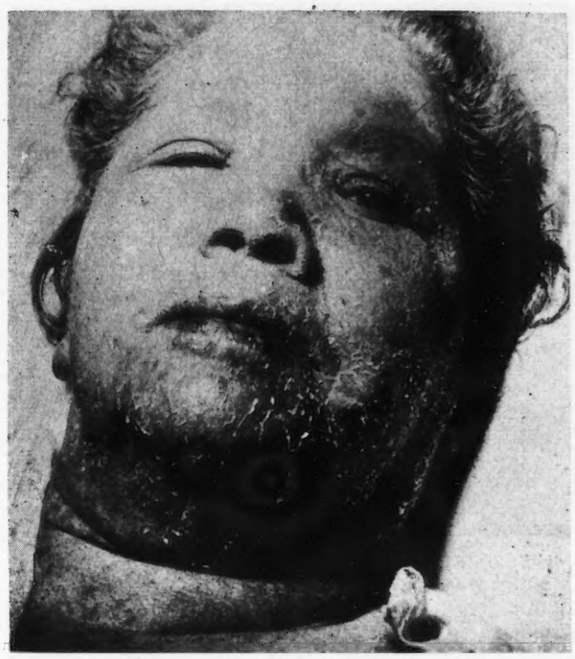

Fig. 2.—Eczematous contact-type dermatitis caused by the local application of penicillin ointment. There is erythema, with œdema and some vesiculation and fine scale.

and a particular drug may cause various types of eruption. It is not common practice to include contact dermatitis due to the external application of drugs in a discussion on drug eruptions. However, this type of eruption is the commonest form of reaction produced by drugs, and it can assume considerable importance, as we have seen in the problem of crossed sensitization. It also merits our serious attention because it is possible to sensitize an individual to a medication such as an antibiotic, by its local application, and thereby deprive the patient of a valuable form of systemic treatment should the occasion arise. Absorption through the skin of a drug like mercury may in exceptional cases lead to kidney damage, and it is thought by some to be a causative factor in the production of acrodynia.

Contact dermatitis due to drugs is an allergic eczematous type of dermatitis characterized primarily by erythema, vesiculation and itching. The location of the lesion and an accurate history will usually suggest the correct diagnosis. This may be confirmed by the application of a patch test, in the proper concentration. Fig. 2 shows a typical contact-type dermatitis produced by the application of penicillin ointment.

Eruptions due to the consumption or parenteral use of drugs may take the form of any cutaneous eruptions that have been described. They may be limited or generalized in distribution, and are usually symmetric.

Urticaria can be produced by many drugs. Penicillin is a very common cause of urticaria; reaction often takes the form of serum sickness, appearing one to two weeks after the exhibition of the drug, and it may be accompanied by a painful arthralgia in the small joints of the hands and feet. It often follows the use of penicillin throat lozenges.

Widespread erythematous eruptions, scarlatiniform or morbilliform in character, present a difficult diagnostic problem. They may be accompanied by fever and may or may not be itchy. This is a very common type of eruption and may be induced by many drugs, particularly barbiturates and sulfonamides.

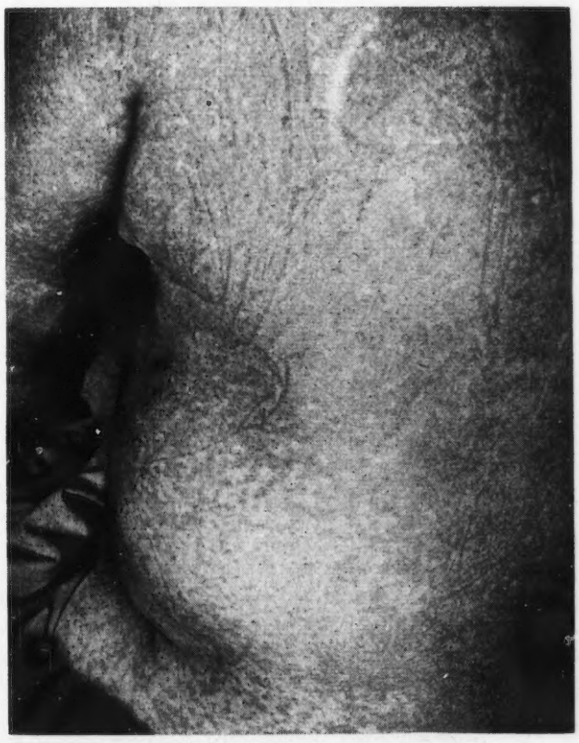

Fig. 3.—Scarlatiniform eruption due to Danilone (phenindione).

Fig. 3 is the picture of a man's back with a generalized scarlatiniform eruption. The rash appeared suddenly after the patient had been on treatment consisting of rest, Danilone (phenindione) and Tuinal (Seconal Sodium and Amytal Sodium) for one month, for coronary thrombosis. Because barbiturates are such a common cause of drug eruptions the Tuinal was stopped first, but the rash persisted. The skin cleared rapidly as soon as the Danilone therapy was terminated.

A generalized morbilliform eruption, with some formation of bullæ, is shown in Fig. 4. This 54-year-old patient gave a history of recurrent attacks of dermatitis of 15 years' duration. Three years previously she had been told not to take any medication containing phenobarbital, and her skin had remained clear during that time. The night before I saw her for the first time, she had taken 1 grain of phenobarbital. She was a very sick looking woman with a generalized morbilliform eruption, which had been severe enough to form bullæ on the back. Her

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sedimentation rate was 122 mm. in one hour; there were 3300 white cells per c.c.; and there were no lupus erythematosus bodies demonstrable in a marrow puncture. She recovered within two weeks on bland local therapy. One hesitates to surmise what might have happened if barbiturate therapy had been continued.

Occasionally this form of dermatitis may go on to a generalized exfoliative dermatitis, with lymphadenopathy, fever, and changes in the blood picture; if the cause is not established early, there may be a fatal outcome.

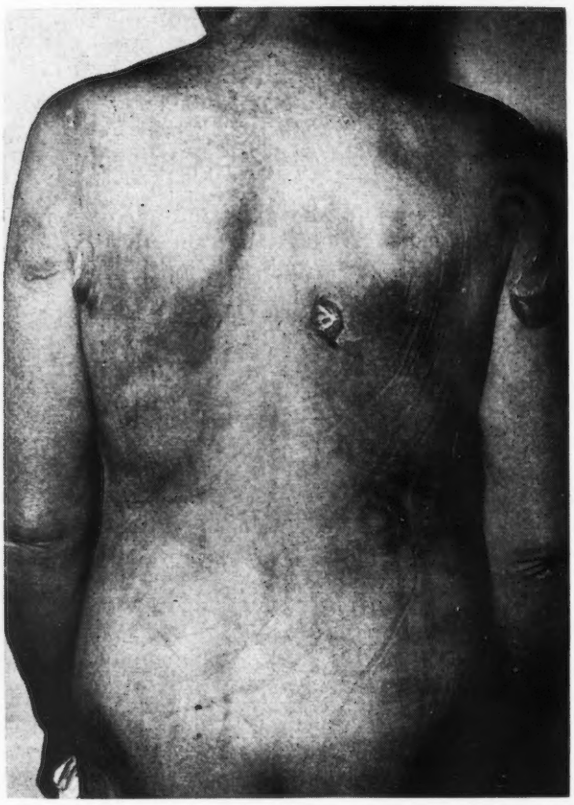

Fig. 4.—Generalized morbilliform eruption, with a few bullæ, caused by the ingestion of one grain of phenobarbital.

This type of drug reaction is illustrated in Figs. 5 and 6. This 53-year-old labourer developed a redness on his left ankle two months before he came to hospital for treatment. Within two days the eruption started to spread over his body. He complained of feeling cold and his whole skin became red, thickened, dry and scaly. The inguinal glands became enlarged and firm. They were not tender. He lost 20 lb. in two months. His blood count was normal; there was no eosinophilia; and the sedimentation rate was 3 mm. in an hour. There were no lupus erythematosus bodies demonstrable in a marrow culture and his blood proteins were normal. A chest radiograph was negative and a skin biopsy was not diagnostic. He was started on bland local therapy, oral cortisone, phenobarbital ½ grain three times a

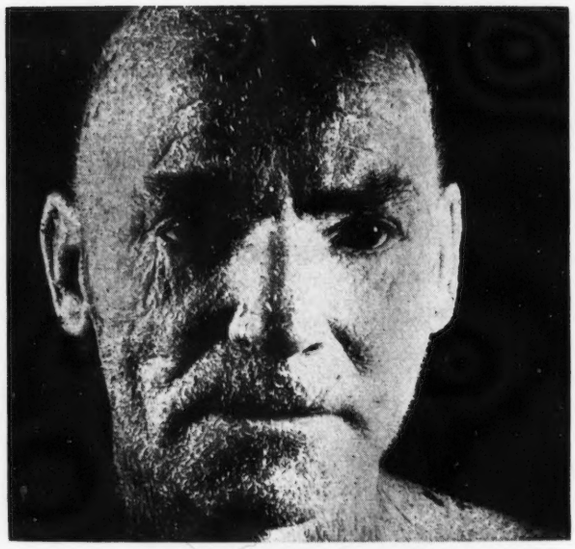

Fig. 5.—Exfoliative dermatitis due to barbiturates.

day, and Tuinal 3 grains at bedtime. He improved a little on this routine, but not completely. After about one month's treatment in hospital the patient volunteered the information that he always felt itchier after taking his sedative at night. He had also noted this itchy sensation when he took a sedative before coming into hospital. All barbiturates were stopped and the patient improved rapidly. Within three weeks he was nearly ready for discharge. Then, as is so often the case in hospital, routine caught up with him, and he was given a grain and a half of Seconal. He had an immediate exacerbation, which took another month to subside.

Vesicular and bullous drug eruptions should be kept constantly in mind in the differential

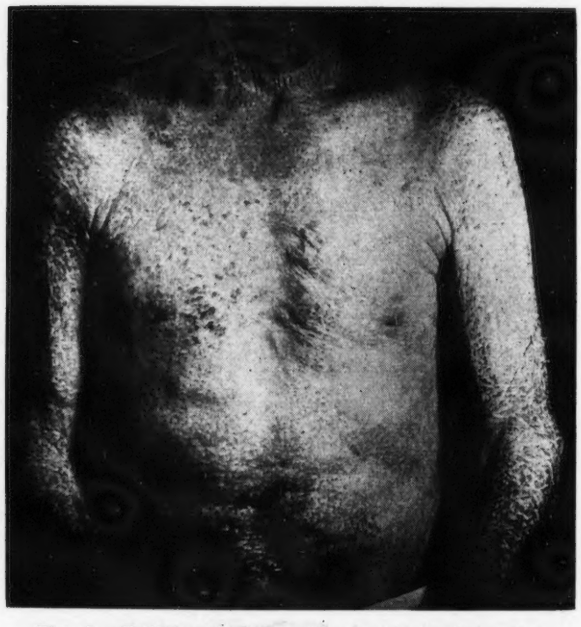

Fig. 6.—Exfoliative dermatitis due to barbiturates.

diagnosis of erythema multiforme, dermatitis herpetiformis and pemphigus vulgaris. Arsenic and halogen drugs, the iodides and bromides, cause this type of eruption most frequently. The halogen drugs also produce acneiform eruptions (Fig. 7) as well as chronic granulomatous masses that have to be differentiated from tertiary syphilis, tuberculosis, blastomycosis and carcinoma.

A purpuric eruption may be the sole expression of drug hypersensitivity. The purpuric eruption on the legs shown in Fig. 8 appeared after the patient had taken Tuinal, prescribed by her physician. We had seen this patient previously for a recurrent eruption on her legs of three years' duration and had suggested she should not take any more barbiturates. Drugs containing carbromal, such as Carbritol, Sedormid and Sedicin not infrequently produce a purpuric eruption. If it is only on the lower extremities, it may be clinically indistinguishable from

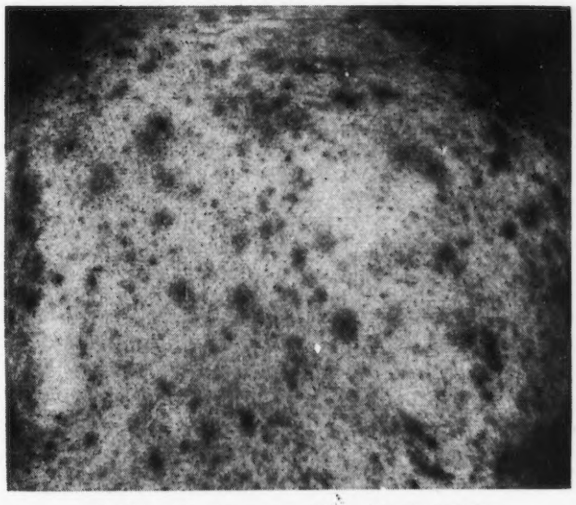

Fig. 7.—Acneiform eruption due to iodide.

Schamberg's progressive pigmentary dermatosis. Until recently the sedatives Sedormid and Sedicin could be purchased without a prescription. Because of its carbromal component, one might expect to see purpura induced by the recently introduced drug, Anatensin.

Fixed drug eruptions are always of particular interest. These lesions are fixed as to site. Every time the causative drug is taken there is a flare-up at the previously affected site. New areas can also be involved, but the older sites always react at the same time. Fixed drug eruptions are usually erythematous and are followed by hyperpigmentation. Phenolphthalein, amidopyrine and the sulfonamides are drugs that commonly produce this reaction. Fig. 9 is unusual because it shows a fixed eruption on the dorsal surface of the foot of a man, caused by amidopyrine. The lesion had the typical purplish hue, and occurred in a young man who

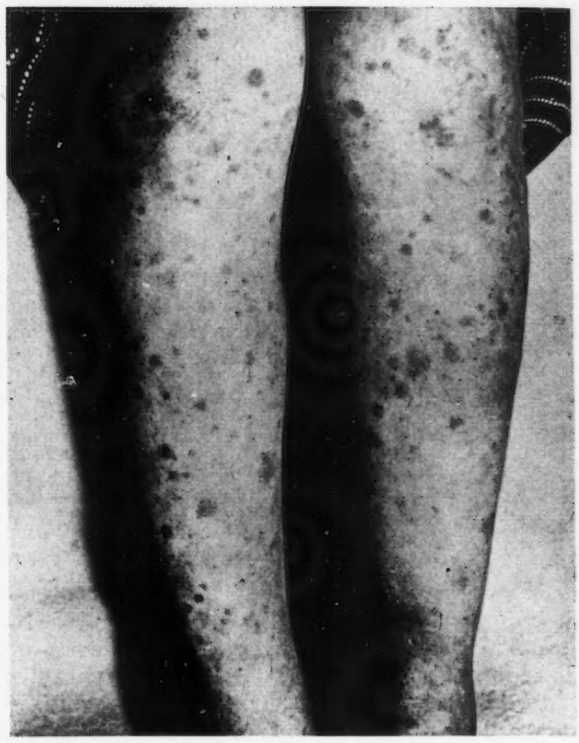

Fig. 8. — Purpuric eruption due to Tuinal (Seconal Sodium and Amytal Sodium).

was taking his sister's Midol tablets to stop his headaches.

Pigmentation of the skin may be produced by heavy metals, such as silver, gold and mercury and arsenic. It is thought that the metals combine with the sulfhydryl groups in the skin and thus remove their inhibitory effect on melanogenesis. Fig. 10 shows the deep pigmentation of argyria. This pigmentation was produced by the prolonged use of eye drops containing silver. A late effect of the administration of organic arsenic is the development of arsenical keratoses on the hands and feet, which are pre-malignant in character. Arsenic epi-

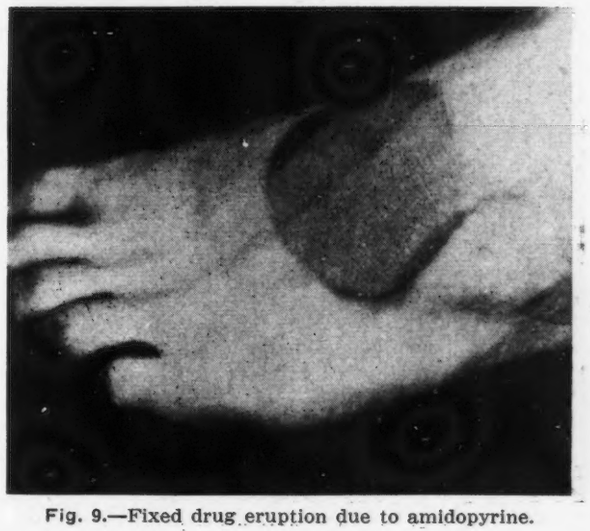

Fig. 9.—Fixed drug eruption due to amidopyrine.

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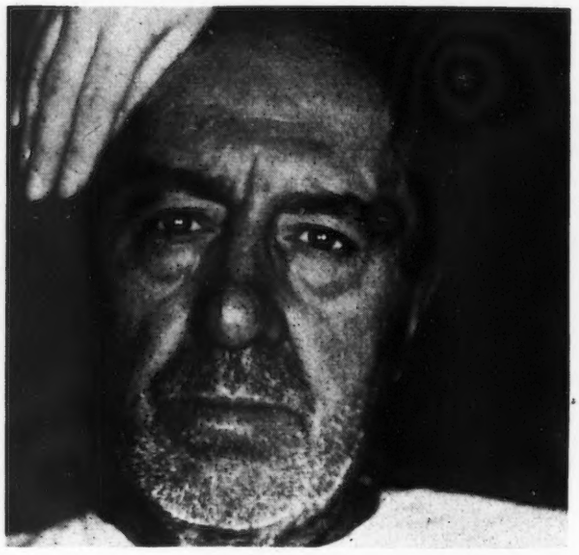

Fig. 10.—Argyria.

thelioma may also develop on the trunk. The arsenical keratoses shown in Fig. 11 were on the foot of a 46-year-old woman. Twenty-five years previously she had been given arsenic by mouth for the treatment of a chronic atopic dermatitis.

Since the advent of penicillin and the broad-spectrum antibiotics a new complication has appeared in drug therapy. Many patients on this type of treatment develop pruritus ani or pruritus vulvæ, which may or may not be preceded by gastro-intestinal symptoms. In some, lesions that resemble thrush develop on the buccal

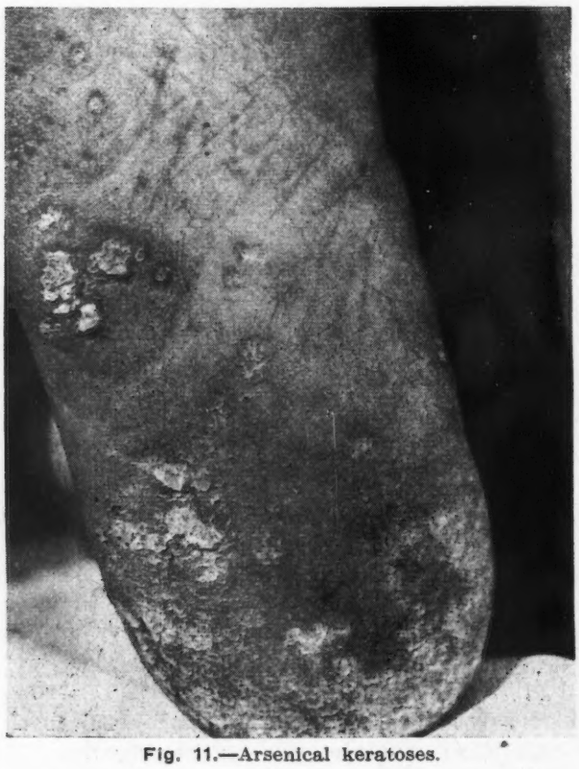

Fig. 11.—Arsenical keratoses.

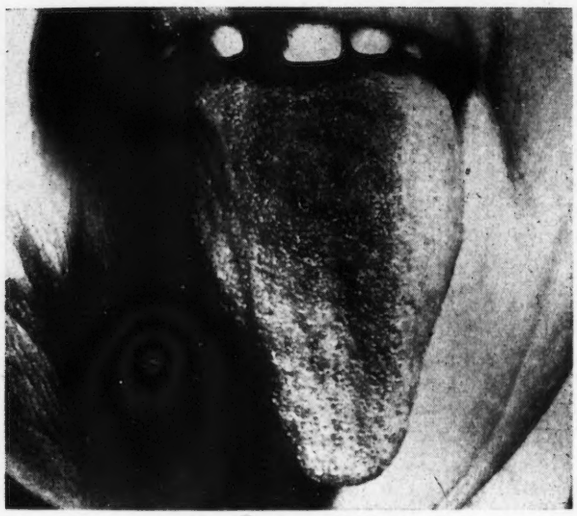

Fig. 12.—Black hairy tongue.

mucosa and the incidence of black hairy tongue has increased (Fig. 12). *Monilia* or *Candida albicans* can often be demonstrated on smears from all of these lesions. It is thought that the antibiotics upset the normal balance between the various micro-organisms, and that if *C. albicans* is present it flourishes and produces lesions. It is still not proven whether *C. albicans* acts in a primary causal role or whether it is entirely saprophytic, invading a suitable soil created by the antibiotic.

Systemic reactions to drugs can only be considered briefly here. Blood dyscrasias associated with drug therapy occur often enough to warrant careful observation of the peripheral blood in all cases of prolonged drug therapy. Anaphylactic shock can be a fatal expression of drug hypersensitivity, and the reported cases of death occurring within a few minutes after the injection of such commonly used medications as penicillin and local anæsthetics must make us thankful that the majority of us have not personally encountered one of these tragic reactions. Bronchial asthma is often produced by aspirin. Hepatitis has long been recognized as a complication of drug therapy. Chlorpromazine and related compounds have caused new interest in this type of reaction. Similarly, it is well known that drugs can produce reactions in the urinary system, varying all the way from a mild hæmaturia to a complete anuria and death. Deafness may be produced by large doses of streptomycin, and peripheral neuritis induced by several drugs. Chronic barbiturism can be an iatrogenic disease and should be constantly kept in mind. It is of particular interest that fever is often produced by drugs, and that fever is the commonest systemic symptom of sulfonamide hypersensitivity.

The changing picture of the practice of medicine is well illustrated by the increased incidence of periarteritis nodosa. According to Alexander, this condition was first described in 1866. Up

to 1931 only 200 proven cases had been reported, and then 350 cases were recorded in 1940-41, after the introduction of the sulfonamides. Sulfonamides have undoubtedly been responsible for more cases of periarteritis nodosa than any other therapeutic agent. Added emphasis is given to the changing pattern of medicine by the excellent paper of Weiss and Swift[7] on the significance of a positive L. E. phenomenon. It is well known that lupus erythematosus bodies may be demonstrated in the bone marrow smears, and in the peripheral blood of patients with acute disseminated lupus erythematosus. They are also found occasionally in certain cases of rheumatic and allied diseases, and occasionally in patients with drug allergy. It is of particular interest that Weiss was able to demonstrate that patients taking hydralazine (Apresoline) may develop a syndrome clinically indistinguishable from acute disseminated lupus erythematosus. It starts with "an arthralgia, and then the patient develops a low-grade fever; the sedimentation rate is raised; there is hyperglobulinæmia, signs of liver and kidney damage, and finally skin lesions resembling those of lupus erythematosus. The L. E. cell phenomenon is sometimes positive." The striking feature of this syndrome is that when the drug is stopped the reaction seems to be reversible.

This presentation of some of the commoner problems encountered in drug reactions is given to draw to your attention the multiplicity of reactions that can occur, and the ways in which they can closely mimic other diseases. There are no tests that will specifically diagnose systemic hypersensitivity to drugs, and patch tests are only confirmatory evidence in local contact reactions. The main diagnostic weapon is a very carefully taken detailed history regarding all types of medication, no matter how they are used, combined with a constant high index of suspicion that drug reactions may imitate almost any condition.

It also behooves us as physicians to prescribe drugs only when they are indicated, and to discourage the use of potentially dangerous substances in self-limited diseases when there is no specific indication for their use. There must always be a calculated risk in prescribing any medication; let us consider this well, before we prescribe.

REFERENCES

1. MAHONEY, J. F., ARNOLD, R. C. AND HARRIS, A.: *Ven. Dis. Inform.*, 24: 355, 1943.
2. O'LEARY, P. A.: *A.M.A. Arch. Dermat.*, 71: 1, 1955.
3. ROSTENBERG, A. AND WEBSTER, J.: *J. A. M. A.*, 154: 221, 1954.
4. ALEXANDER, H. L.: Reactions with drug therapy, W. B. Saunders Company, Philadelphia, 1955.
5. LANDSTEINER, K. AND JACOBS, J.: *J. Exper. Med.*, 61: 643, 1935.
6. MAYER, R. L.: *J. Allergy*, 20: 159, 1949.
7. WEISS, R. S. AND SWIFT, S.: *A.M.A. Arch. Dermat*, 72: 103, 1955.

Men and Books

A TRIBUTE TO COLIN RUSSEL*

WILDER PENFIELD, O.M., M.D., *Montreal*

THIS IS THE Colin Russel Memorial Meeting of the Montreal Neurological Society. His friends, Mrs. Russel and other members of his family, and his colleagues from near and far are gathered here to pay him the tribute so justly due. The first paper will be read by Dr. William Francis and the second by Dr. Francis McNaughton who has planned this meeting.

William Francis is Librarian of the Osler Library, a celebrated scholar of medical history and literature. No one could speak more eloquently of Colin Russel—The Man, for they were friends and companions during many years of peace and war.

In the spring of this year a remarkable testimonial dinner was given to Dr. Francis. It was a sort of Franciscan feast in which the spirit of Sir William Osler seemed to join and to rejoice in our tribute to his much loved nephew. In the midst of his own speech, Francis broke off to hail one guest, and one guest only, among those who filled the great dining hall.

"Colin Russel," he said, "you should be here in my seat of honour, and I in your seat."

He spoke with a premonition that none of us understood. It was only a few days later that Colin Russel left his tired body, finishing off the term of service that the good Lord had given him.

The second address will be delivered by Francis McNaughton, a pupil of Colin Russel, and his successor as Neurologist-in-Chief at the Royal Victoria Hospital and the Montreal Neurological Institute. He possesses the qualities most important for great leadership: He is wise as he is modest. He is a sound scholar of the Classics, a thoughtful anatomist and a good physician and teacher. He understands, as Osler did, but as very few others have done, the miracles that may be wrought by the "milk of human kindness".

Allow me, as chairman, to add a word of tribute to Colin Russel, for I knew him well, and loved him. He was the pioneer in a new field. It was difficult, discouraging work to force the profession, the public and the University to recognize the existence of a new medical specialty, especially, I like to think, before he had the help of neurosurgical colleagues. But the dawn of a new day has come and his pupils, Francis McNaughton, Preston Robb and many

*Chairman's Remarks at the Colin Russel Memorial Meeting in the Montreal Neurological Institute, on October 10, 1956.

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others in far-off parts of the world have embarked on a career of great service to mankind. The volume of work done by neurologists has doubled and redoubled since the days of Robbins and Russel and McKay.

We must recall today the names of other brilliant neurologists, who were pupils of Colin Russel but who died before their time: Norman Petersen, John Kershman and Donald McEachern.

In a sense it may be said that most of us on the clinical staff of this Institute are Russel's pupils in neurology, as well as his friends. When I went to work as a student at the Queen's Square Hospital in London in 1920 I heard much of the young Canadian who had been resident physician there, especially from the man who became his life-long friend, Gordon Holmes.

When William Cone and I came to live in Montreal, Colin Russel greeted us in his blunt, warm-hearted way. Like the football player he had been, he seemed to say, "If you young neurosurgeons are good enough for this rough-and-tumble, come on in and hit the line hard." At my first visit to Montreal, we met and I remembered that he chuckled and looked at me with a glance I came to know so well, "All brain tumours in Canada," he said, "are malignant. The benign, removable variety grows only south of the Canadian border."

When the Montreal Neurological Institute opened its doors in 1934, Colin Russel stood with Cone and me in the place of leadership. He was elected President of the American Neurological Association that year and brought it to Canada for the first time. It was, I suppose, the largest and most important association of its kind in the world.

When the Great War began, in 1939, Colin Russel immediately proposed to the Army Medical Directorate in Ottawa the formation of a Canadian Army Neurological Hospital. His plans were accepted and he led the unit overseas.

He was the founder of Neurology in the Montreal Neurological Institute, a careful clinician, an inspiring teacher. He was also a good companion, an explorer, a soldier and a gay troubadour.

As Director of this Institute, I hope that money may be found to establish a Colin Russel Lectureship here, so that a series of lectures may recall his name as long as there is an Institute and a University.

He had a little habit which we all remember, a habit of exclaiming "Bless you." And we say now, "You are much missed among us; 'bless you', Colin Russel."

COLIN RUSSEL, THE MAN

W. W. FRANCIS, M.D.,* *Montreal*

IT IS NOT POSSIBLE to speak with critical detachment of one's intimate friend of 54 years, so you must pardon me if I bring myself too much into the picture and seem to his virtues very kind and to his faults a little blind. Certainly the former were many and the latter few. Colin Kerr Russel was more than fortunate in his parents, Montrealers of good family on both sides. Born on February 4, 1877, he had entered on his 80th year at his death on March 4, 1956. His middle name, the surname of his maternal grandmother, is the Scottish K-e-r-r, "care", not the English "car", let alone the mongrel "cur"! He was educated, like all good Montrealers of the time, at the High School, and also at the private school of Mr. Curry, "Old Bolivar" as we called him at Port Hope before he was lured to Montreal. Apparently as a young boy he had announced that he was to be a doctor and, wanting to be a good one, he entered McGill in 1894, taking the arts course first, which was neither obligatory nor usual at the time, and graduating B.A. in '97 and M.D. in 1901.

During his summer holidays he worked with A. P. Low on the geological survey. Of the 1895 expedition, north of Lake Superior and returning via Winnipeg, I find no record, but the next year he was one of three anonymous "canoe-men" who with three named scientists were the first white men to cross the Ungava peninsula in canoes. Low's Report for 1896, entitled "Traverse of the Northern Part of the Labrador Peninsula from Richmond Gulf to Ungava Bay", is in vol. 9, 1898, of the Geological Survey of Canada, and has been reprinted frequently by the Quebec Government in "Extracts from Reports on . . . Ungava or New Quebec". It is a purely scientific document, devoid of human interest of which there was really plenty. They left Ottawa May 27, arrived at Moose Factory on James Bay via the C.P.R. plus 350 miles of canoeing and portaging and spent 16 perilous days sailing across Hudson Bay and up its east coast in a boat too low in the water for comfort or safety. The crossing of Ungava by canoe took more than two months, until September 5; then there were long waits at Fort Chimo for a steamer to Hamilton Inlet on the Atlantic coast and for a schooner thence to Quebec. The wonder was not that Russel arrived very late for the session but that he was in time to play in a football match the next day. Half way across the peninsula there was a delay which nearly broke up the expedition. Low was a remarkably capable man, but not too genial. In a stand-up fight with the chief Indian guide he suffered a long gash in the

*Osler Library, McGill University, Montreal.

leg, which he calmly sewed up himself with a continuous suture and nearly died of the resulting infection. Colin, as prospective physician, and like Jacques Cartier at Quebec, took the advice of the repentant Indian and successfully treated the wound with a decoction of the inner bark of the tamarack and poultices of caribou marrow. They were short of ammunition but not of provisions; the caribou were plentiful in those days; the Indians would drive them into the water, overtake one in a canoe and deftly sever a renal artery with one jab of the knife. In the *Gazette* three years ago some of you may have seen a picture of Colin looking on while some Arctic experts retraced for him his route on a modern map. Among them was our Dr. Ray Lawson, who helped to jog Colin's fading memory and who has reminded me of some of the above details. All that my low mind remembered was the daily disappearance of the Fort Chimo cat and Colin stalking her. After a mile or so of barren rock he solved the problem of what she was hunting—the nearest patch of loose earth for feline hygiene!

It is interesting to read that Frank Scrimger, our still lamented surgeon and V.C., also went on one of these surveys during his arts course and was left behind to look after the cook with some acute abdominal condition. His instructions were to apply hot fomentations and keep them hot. With characteristic thoroughness the resourceful Scrimger not only brought the fellow out alive, but seriously scalded both his own hands, and on his return decided to study medicine instead of the law for which he had been intended.

I came under Colin's spell when he was a senior and I junior intern under James Stewart at the R.V.H. in 1902-3. His most obvious virtue, I think, was his unfailing kindness. He was more or less responsible only for me, but other raw housemen have told me how he went out of his way to make things easy for them too. We learned something of diseases, especially nervous ones, from Jimmie Stewart, in spite of his having, as Osler said, not the gift but the infirmity of taciturnity. One Saturday afternoon Colin and I went page by page through the last section of "Osler" and finally got light on a strange case. We went up to the ward, put the man through the tests, and there could be no doubt. When Colin suggested the diagnosis, Dr. Stewart countered in his ancestral broad Scots with "Gawd! what made ye thenk o' thot?" No verbal confirmation until ten days later when, as he was getting into his carriage, he said, "I'll show that case of myasthenia gravis at the Medical Society tomorrow." Nothing much escaped him. There was a neurotic lad whom he hypnotized with ease and with benefit. Once in the chief's absence Colin tried the trick and failed to put him under. So did Dr. Stewart at his next visit. He looked searchingly at our would-be poker faces and said sorrowfully, "You have upset my apple-cart."

The only fault I remember in this friend who grappled me to his soul with hoops of steel was a certain stubbornness. As a patient he was unmanageable. When he came down with typhoid during a mild epidemic among the Hospital staff, he insisted on having his head shaved as soon as his temperature reached 102, whereupon it promptly fell to rise no more. Then hunger set in, but the unbreakable rule was no solid food for two weeks. At dead of night he raided the ward larder and devoured half a chicken, so we sent him home with a bad mark and a bottle of mock hair-restorer. A touchingly grateful Chinaman, alias Ping Pong, whom we had saved from a very watery dropsical grave, invited us to Chinatown for their new-year celebration but came back a few days before the date and begged us to stay away as there was a Tong war brewing and sure to be shooting. And there was, with plenty of murder. Colin provided himself with a revolver and refused to be dissuaded, but a lucky emergency kept him on duty. At Christmas he organized an impromptu dance in a vacant ward. It was raided by Webster, that active prince of snooperintendents, and Colin was reprimanded by the Board. What happened to the nurses I don't remember; doubtless "something with boiling oil in it".

Most of the next three years was spent in postgraduate work, first at Johns Hopkins in neurology and psychiatry. There he endeared himself to the Oslers and others. Then on the Continent, mostly at Zurich in the neuroanatomical institute of von Monakow whom he revered as his master and whose life he wrote for the Foundation Volume of our M.N.I. For most of 1905, at the end of which year he returned to Montreal, he was a fellow-intern with Gordon Holmes and Kinnier Wilson at Queen Square, London's neurological Mecca. He was too busy for much companionship when I became an extern at nearby Great Ormond St., but he introduced me to a good boarding house and one of its denizens, a medical student who became a lifelong friend of us both and is now Sir Arthur S. MacNalty of the Ministry of Health and editor of the medical history of the War.

During the years of waiting for practice—shorter for him than for me—we had plenty of unremunerative work at the R.V.H. and McGill, and plenty of good skiing on the Mountain at the week-ends, the Laurentians being still unexploited. Once (never again) I even played his favourite golf with him on the then wilds of Westmount Mountain. Here I must pay tribute to his family who all opened their hearts and homes to me. His father was a well-read, soft-spoken and courteous gentleman of the old school. The prosperous steel business

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which bears his name, Hugh Russel and Sons, and is now run by his grandsons, was inherited from his father-in-law, his wife having been Jane Evans. She was a lovable, gentle soul with a fine sense of humour. Colin and I had five-o'clock tea with her whenever possible, while his father would chaff us for being such old women. But one bad summer day when I needed consolation I called on him when he was alone in the house. I blurted out my news and he guessed I was hard hit. He leapt from his chair, threw an arm round my shoulder, and said, "Come down to the kitchen and we'll make a cup of tea." That unconditioned reflex was more consoling than the tea and it warmed my heart to the dear man for ever. My own mother in Toronto—they get strange ideas—accused me of working too hard, but when I sent her an hourly schedule, she retorted, "Well you may not hustle all week, but you seem to Russel all Sunday." Unlike Colin, his father was an ardent churchgoer, and I think Mrs. Russel was grateful to me when I came to Sunday supper and took her place in accompanying him to evening service. He had been a Presbyterian but became an Anglican, as was his wife, after a difference of opinion with his minister and next-door neighbour, the grandfather of our Dr. Philip Hill. Colin and his dog both would bristle when they met the stately figures of Mr. Hill and his dog, but this was canine, not theological odium, the medical setter having once been chewed up by the reverend mastiff. It is interesting that Colin retained an affection for the Shorter Catechism and consequently two of its clauses were read at his Anglican funeral, but I think that his pia mater was no more stretched than was Sir Thomas Browne's by "those wingy mysteries in divinity". Predestination may once have bothered him. His mother told me this story about one of his brothers who vehemently denies it, so I pin it on Colin. He was in the corner doing penance for the small boy's usual crime: "Mother, if I died and the angels took me up to Heaven and just as we got there I said a bad word, would they let me drop?" It would have to be an extremely bad one, for his, I'm sure, was the "pure religion and undefiled" of St. James, visiting the afflicted and keeping himself "unspotted from the world".

In 1909 he had the best of all possible luck; he married the right girl, Evelyn Molson, the youngest sister of Herbert and Percival. This might well have been a loss to me, but instead I acquired a new circle of friends, including gradually five pseudo nephews and nieces nearer and dearer than the genuine variety. He served with distinction in both wars. In France in 1915 with the McGill Hospital he had little to do except exercise the colonels' horses, but most of our specialists (except the obstetricians!) were later properly employed, Colin being neurologist to the Ramsgate Hospital. There his young family joined him until the hit-and-run raids became too menacing, when the wife and children settled in Oxford, thereby spoiling the baby's fun, who had chuckled with delight at each *boomp*, as she called it, on the beach or in the cellar.

A year or two before the second war he was seriously ill with a lung condition until the bronchoscope revealed a tumour which proved to be benign and was excised at Philadelphia by one of the Jackson wizards. This did not prevent his joining up again in 1939 at the age of 62 and serving three years, the last two in England, as Colonel and consultant both to the Canadians and British.

On his return to Canada at the statutory age of 65, his retirement was postponed for a couple of years. Even so, superannuation is always a wrench when one still feels capable, and it is hard for an old doctor to have to move into a new office and watch his powers and his practice decline. After a very happy life he was denied the crowning blessing of a serene old age. "Call no man happy till he's dead!" He never was the contemplative sort, and his increasing disabilities, irremediable blindness, confusion, arteriosclerosis, cut him off from his hobbies, reading, painting, golf, fishing. Worst of all, he harrowed himself and friends with an obsession that his long services had never been recognized by his hospital and university. It has not been my charge to speak of his professional and academic work, but it surprised me to learn that the highest rank he attained was associate professor, and if, as he said, in all those 50 years he had never sat in at a Hospital or Faculty meeting, he may well have had a grievance. It is on my conscience that I never stirred up an agitation to have him granted some sort of emeritus title or honorary degree which might have appeased him. But my own outlook seemed precarious till last February when a superiority complex was conferred on me by certain "Tributes" of which the warmest and best was Colin's, in the opinion of a librarian who had never heard of him. It makes me wonder whether these memorial meetings should not be reserved for the untimely dead, like Norman Petersen, Donald McEachern and John Kershman, and an ante-mortem superannuation party be substituted to eulogize the despondent 66-year-olds.

Perhaps I may claim that there is only one person here who can more sincerely quote these lines from "In Memoriam":

> Whatever way my days decline,
> I felt and feel, though left alone,
> His being working in mine own,
> The footsteps of his life in mine.

Blessings on his memory, and may he rest in peace!

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COLIN RUSSEL, A PIONEER OF CANADIAN NEUROLOGY

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I AM glad of this opportunity to review with you the career of my teacher and colleague, Dr. Colin Russel, and to say something of his contributions to neurology. Let me remind you at the outset that Colin Russel, the gay and charming person whom Dr. Francis has described, was the same person in his professional life.

Dr. Russel was educated at Montreal High School and took his B.A. at McGill in 1897 and his M.D. in 1901. His first two postgraduate years were spent as an intern in the Department of Medicine at the new Royal Victoria Hospital, which had opened its doors in 1894, only seven years before his graduation. Clinical neurology at that time was an integral part of medicine. While some physicians took a lively interest in neurological problems, there was no one at McGill who specialized completely in the neurological field, though the need was becoming clear.

At the end of his internship, Dr. Russel decided, with the encouragement of his McGill teachers, to undertake the study of neurology, and started on his special studies with a period as extern in neurology and psychiatry at the Johns Hopkins Hospital, Baltimore, under the direction of Dr. William Osler. Undoubtedly Osler helped to map out his wise plan of European study — which took him first to Zurich in 1903-1904 to the Institute of Professor von Monakow, who was then approaching the height of his career. At Zurich, he studied the anatomy and pathology of the nervous system — and came in contact with von Monakow's important discoveries regarding the anatomy of the visual system, and the brain stem. In later years Dr. Russel often spoke in admiration of the great professor, and in 1935 he contributed a biographical article on von Monakow to the first Foundation volume of the Montreal Neurological Institute.

Following his study period in Zurich Dr. Russel spent some time in Berlin, attending the clinic of Professor Oppenheim, then the most famous of German neurologists. From there, he moved to Paris, where French neurology was in full flower. One can imagine the intellectual stimulation he would gain from attending the clinics of teachers such as Déjèrine Pierre Marie, and Babinski!

Finally in 1905, he arrived in London, to spend a full and eventful year as intern at the National Hospital, Queen Square, which had the forbidding title, "The National Hospital for the Relief and Cure of the Paralysed and Epileptic". This year of clinical training undoubtedly was the most important influence in his professional life, for his interests were predominantly clinical, and here he came in touch with the group of men who established the worldwide fame of British neurology. Hughlings Jackson, then a man of 70, had retired from the active staff but still had hospital beds of his own and visited the hospital at irregular intervals. Ferrier and Gowers were active still, also Beevor, Batten, Taylor, Risien Russell, and Turner. James Collier and Gordon Holmes were younger staff members. Sir Victor Horsley, the pioneer of British neurosurgery, was 48 and at the peak of his career. This was indeed "the Golden Age of British Neurology", as Sir Gordon Holmes has named it in his history of the National Hospital.

Col. C. K. Russel at No. 1 Neurological Hospital, Basingstoke, 1941.

Colin Russel must have turned his back reluctantly on Queen Square when he returned to Montreal in 1906 and faced the problems of clinical practice and teaching. He became Clinical Assistant in Medicine and Neurology at the Royal Victoria Hospital in the year of his return. From that point onward, his career was one of rapid advancement, both in hospital and in university appointments. In 1910 he became Neurologist to the Hospital, in 1913, Lecturer in Clinical Neurology at McGill, and in 1922, after the First World War, Clinical Professor of Neurology.

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At this point in my story, I would like to follow Dr. Russel's neurological career through a review of his contributions to the medical literature. Medical writings reveal only one aspect of a man's career and activities, but they do show up his major interests and his intellectual approach to problems.

I have found particular interest in reading over Dr. Russel's articles which appeared during the long stretch of 30 years before I first knew him as a teacher at McGill. They help me to realize the extent of his experiences and his interests over this period—and to trace their continuity into the later period of his life with which some of us are more familiar.

There are several interesting early reprints dating from his internship at the Royal Victoria Hospital, dealing with perforation in typhoid fever, and with unusual varieties of pulmonary disease. These articles reveal an alert clinical interest, careful observation, and independent thinking. It is worth mentioning that in 1903, he was able to review 857 cases of typhoid fever from the Royal Victoria Hospital records, although the wards had been open for less than ten years.

Two important publications represent the first fruits of his training at the National Hospital. In 1906 he published an article in *Brain* with Sir Victor Horsley, entitled "Note on apparent re-representation in the cerebral cortex of the type of sensory representation as it exists in the spinal cord". This was a study of the cortical sensory changes observed in a group of six patients — before and after operative removal of expanding lesions in the sensory cortex. It provided evidence for a segmental representation of tactile sensation and topognosis in the Rolandic or sensorimotor cortex of man, an important conclusion which was verified only years later by more accurate methods. (I have in mind particularly the monograph by Drs. Penfield and Rasmussen which appeared in 1950, some 44 years later.) It is interesting to realize how fragmentary still was the evidence for functional localization in the human brain in 1906. Campbell's famous monograph on "The localization of cerebral function" had appeared just a year earlier, and was provoking a great deal of discussion and research.

The second neurological paper, on "The visual fields in cases of indirect or incomplete lesions of the optic system", published in 1906 in the *Journal of Nervous and Mental Diseases,* presented the analysis of a series of six patients observed at the National Hospital with changes in the visual fields. It summarized in a very clear fashion the intricate anatomy of the visual system, and correlated this with changes observed in each patient. While this paper contained no new concepts, it is still, after 50 years, an admirable clinical presentation, to which one can add little.

There follows a series of shorter clinical papers, concentrated particularly into the first five-year period after his return to Montreal. Dr. Russel was always interested in cervical rib syndromes, and in 1907 published a series of cases, including one to which he often referred in later years. This was the case of a young woman who, as a result of a cervical rib, developed an obliteration of the subclavian artery—with subsequent gangrene of the fingers. He studied her case with Dr. Archibald. In his clinical summary of the patient's case, I find a characteristic phrase, worthy of quotation. "Apart from the fact that she was stupid and neurotic, the nervous system was normal."

Another paper of historical interest now presented a case of endothelioma invading the base of the skull and the left temporal lobe, with a three-year history of "dreamy states". At the outset of each attack the patient experienced a feeling of dread, and began to tremble. Then she would see as if in a dream a woman trying to save a child from drowning. There was no experience of an unusual smell or taste. A case of Hughlings Jackson was recalled, as well as a similar case observed by Dr. Russel at Queen Square. (This is of interest now to compare with recent work from this Institute on temporal lobe epilepsy.)

Another excellent paper, read before the Canadian Medical Association in 1910, reviews his personal experience of 38 cases of acute poliomyelitis, observed during an outbreak in 1909, including two postmortem examinations. At that time, the characteristics of the disease in its epidemic form were just being generally recognized, and two young American workers, Flexner and Lewis, had only a few months earlier demonstrated that the disease could be transmitted through monkeys and was probably due to a virus.

Many of you will recall Dr. Russel's interest in Edinger's exhaustion theory of tabes dorsalis, an interest which he maintained throughout his neurological career. According to this theory, the syphilitic toxins lodge in those parts of the nervous system which are used most by the affected person, and this determines the site of the major lesions. To illustrate the correctness of this theory he presented the case of the dining-car chef, on his feet all day, who developed ataxia of the legs with tabes. The tailor, on the other hand, who sat all day, threading his needle, developed ataxia and pains in the arms or the cervical form of tabes. When eyestrain was prominent, optic atrophy developed, and so forth.

In 1912 he published an article on the subject, in which he presented his only piece of experimental work—which was planned to put Edinger's theory to the test. He obtained two rabbits, which had been inoculated with the *Spirochæta pallida,* and exposed these unfor-

tunate animals to alternating light and darkness, by means of a "miniature revolving lighthouse" which he had devised. Both infected animals developed a dilated pupil, inactive to light, while a control non-infected animal, subjected to the same alternating light and darkness, did not. Dr. Russel felt that he had produced something close to an Argyll Robertson pupil by this method and had proved Edinger's theory, but unfortunately never followed it up with more practical experiments.

With modern control of syphilis, tabes is fast disappearing as a neurological disease, and with it has gone our interest in Edinger's theory, but the problem of the pathogenesis of tabes is still unsolved, as it was in 1912, and some day we may face Edinger's theory anew.

The First World War brought an abrupt change in Dr. Russel's career and a new field of neuropsychiatric experience. As an officer in the R.C.A.M.C. he served in Canada, England and France and was for a time in charge of neuropsychiatric patients in the Army Hospital at Ramsgate where he was called on to treat many puzzling neurological and psychiatric states which had at first been lumped together under the general term of "shellshock". It was this work which in 1917 earned for him a citation by the War Office in London "for valuable services rendered in connection with the War". His experiences and his views on the war neuroses are well stated in a series of papers which were published in the *Canadian Medical Association Journal*, and later summarized in an address before the American Medical Association in 1919. It is interesting to find, on re-reading these papers, what little change is necessary in his basic concepts to fit the experiences of the Second World War.

Peace in 1918 brought rehabilitation and changes. Rapid advances in the techniques of neurosurgery took place during and after the war. Dr. Archibald had carried out what little brain surgery was done at the Royal Victoria Hospital in the pre-war years, and realized more and more the need to develop the field of neurosurgery in Montreal. In 1928 came the reorganization which brought Dr. Penfield and Dr. Cone to Montreal as neurological partners with Dr. Russel and gave to neurology a new impetus.

In 1934, the Department moved to its new quarters in the Neurological Institute, and the following June, 1935, the Institute played host to the American Neurological Association, with Dr. Russel as its President. At the time, he stated that this was simply a recognition of the importance of the new institute. However, his selection as President was in fact a great tribute to Dr. Russel himself and his services to neurology over a period of nearly thirty years. He had played an active part in the Association from the time he became a member in 1909, and had many close friends among its membership. It remained a major interest throughout his life, until in later years ill health interfered with his attendance at annual meetings.

Of all the medical societies to which he belonged, he took greatest pride in the A.N.A. and in his honorary Fellowship in the Royal Society of Medicine of London.

He chose as the subject of his presidential address the career of Dr. James Douglas, a pioneer physician, surgeon and alienist of Quebec City in the 19th century. Among other notable achievements Dr. Douglas organized the first modern mental institution at Beauport in 1845 at a time when in many countries insane persons were still being restrained in jails and similar institutions, in some cases being chained to the floor or wall. It is easy to understand why Douglas, with his background of world travel, colourful adventure and medical pioneering, appealed to the adventuring spirit in Colin Russel.

The time from 1928 up to the outbreak of war in 1939 was a fruitful period of collaboration in building the new Department of Neurology and Neurosurgery, and I am certain that this was one of the most deeply satisfying experiences of his life. He was the oldest and most experienced member of the department, seasoned by wide clinical knowledge gained in both peace and war. He brought ripe wisdom and perspective to the clinical activities of the Institute as it gradually took shape. Although very much of an individualist, he contributed a great deal to the strong team spirit which grew during that period.

During these busy years a number of his most important papers appeared. In 1931 his article on "The syndrome of the brachium conjunctivum and the tractus spinothalamicus" was published. This was an almost unique clinical pathological report of a case of thrombosis of the superior cerebellar artery. He was able to correlate the neurological signs very closely with the anatomical lesion in the tegmentum of the midbrain. It is of interest to note that when Dr. Earl Walker in 1942 wrote his well-known report on the relief of pain by mesencephalic tractotomy in man, he based his procedure partly on the findings in Dr. Russel's case.

Other excellent papers were on "The syndrome of the posterior inferior cerebellar artery", published with Dr. George Stavraky, and on "Spontaneous subarachnoid hæmorrhage and brain tumour", written with one of his most brilliant pupils, the late Dr. John Kershman. In 1934, in collaboration with Drs. Cone and Harwood, he published a study of the role of lead as a possible cause of multiple sclerosis. This provoked a great deal of interest and discussion in neurological circles, though it failed to

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establish the hypothesis that lead is a factor in the causation of the disease.

When the Second World War began in 1939, Dr. Russel promptly enlisted in the active forces although he had passed the age of 62, and threw himself into planning activities with the vigour of a man half his age. When the idea of a Canadian Neurological Hospital with the Army Medical Corps was still a dream, Dr. Russel did much of the patient spade-work necessary to convince the Army authorities at Ottawa that this was an improvement on the old hospital organization dating from the First World War. He reviewed his old experiences with the war neuroses and applied this knowledge to the planning of the new hospital. With Dr. Cone and Gordon Holmes, his colleague and friend from Queen Square days, he took part in selecting Hackwood House, Basingstoke, as the home of No. 1 Canadian Neurological Hospital, R.C.A.M.C., and when it was finally established, he became the first Officer Commanding of the Medical Division, with Dr. Cone in charge of Surgery. Of this period, one of his junior officers, Dr. Clifford Richardson of Toronto writes, "Some of my most vivid and cherished memories of the war are experiences with Col. Russel at Basingstoke in 1940 and 1941. He was such a wise and kindly and experienced chief! His wealth of experience with neuroses in World War I was of great value to us. Even the wire brush treatment in Dr. Russel's hands was most effective for the occasional unfortunate recipient." And again, Dr. Richardson writes, "He was a dignified, sound and much respected Army consultant. We younger officers at 'The Neuro' were proud of Col. Russel as our chief, and we missed him greatly when his age and health forced retirement."

Some reference should be made to the paper published in *Lancet* in 1941 by Dr. "Bill" Stewart in collaboration with Drs. Russel and Cone, entitled "Injury to the central nervous system by blast — observation on a pheasant". One night several bombs fell on the hospital grounds at Basingstoke, and the following day, a pheasant was found nearby standing with dejected appearance and closed eyes. When examined, it showed certain catatonic features. After a compromise agreement with the gamekeeper, there was an opportunity to study in the laboratory at Basingstoke the effects of blast upon the nervous system of the unfortunate bird. Although the evidence was inconclusive, this study cast some light on the complicated mechanism of blast injury, a problem which is still far from settled today.

On his return to Canada, Dr. Russel resumed his duties at the Neurological Institute and only gradually retired from its activities in the post-war years. Even when ill health and the burdens of age interfered with his life, he usually managed to attend Monday ward rounds, and executive meetings, and contributed vigorously and emphatically (sometimes with mild profanity) to the discussion of important issues. He resented every inroad that ill health made on his activities. Frequently the spirit protested against the limitations of the body.

So far, I have tried to outline some of the more significant contributions of Dr. Russel to neurological knowledge. What of Colin Russel the physician? What was his relationship with his patients and his students? His approach was authoritative but kindly, probably influenced by his army experience. At times his words might be sharp, but the fatherly twinkle in his eye was rarely absent. He enjoyed his patients and could take infinite pains in caring for them. His patients, in turn, respected and loved him. He liked to teach, and his ward rounds were enjoyable and stimulating. The unhurried philosophical discussions which were so apt to follow morning rounds are still remembered by his old house physicians. He was open to new ideas, and never lost the adventuring spirit of his youth.

One of the hobbies which he developed over the years was the use of motion pictures to record various types of motor disorder. He used these films very effectively for teaching. When he retired, he donated his valuable collection of films to the Institute, and they are still in use. He also collected a large group of teaching slides illustrating neurological disorders.

One particular patient's story should be recorded here. One day in April 1919, a first-year medical student was admitted to the service of Dr. Cushing with progressive weakness of the legs. Dr. Russel was called in as neurological consultant and a diagnosis of Landry's paralysis, or multiple neuritis, was made. Over the next few days, the paralysis advanced to involve the arms, the face, and the muscles of the throat. Finally the respiratory muscles were threatened. These were the days before mechanical respirators, and Dr. Russel prepared to organize the lad's medical classmates into teams to administer artificial respiration, but fortunately this was not necessary. Recovery was slow but complete, and the student was able to resume his medical course the following year and graduated.

Many years later the former patient, Dr. H. W. Trott, wrote his memories entitled "Campus Shadows" and included several vivid chapters on what might be called "Landry's paralysis from the inside". He pays a great tribute to Dr. Russel, who supervised his treatment very attentively and encouraged him to go on, when everyone else seemed to have lost hope. Here are his own words: "God's eternal blessings on Dr. Russel! Only he, in all those long months

of Hell, ever really understood. He talked to me directly every time he came into the room. He stood beside my bed and spoke to me as though he *knew* I could hear him, as though he commanded psychic power to read my thoughts. He answered many an unasked question which my tormented mind wanted to ask. He told me each day that I was doing fine. 'Don't give up, Trott, old boy — keep the chin up and keep fighting'."

As a result of his experiences with the neuroses of the First World War, Dr. Russel was very interested in hysteria and all the shadowy gradations between hysteria and malingering. Reference has already been made to the wire brush, which he sometimes employed to "encourage" and "persuade" a patient with hysterical paralysis to regain the use of the affected part. He combined its use with strong suggestion, and a stern but fatherly approach — a little reminiscent of the Biblical statement that "Whom the Lord loveth, him he chasteneth." He did not approve of hypnotism in treatment, and had no faith in it.

Some of you will undoubtedly remember his optical detective (as he called it). This was a peep-hole box which he designed when overseas during the First World War, to detect monocular blindness in hysterical or malingering soldiers. By means of a clever arrangement of mirrors, a test object inside the lighted box appeared to be viewed by the patient's good eye, when in fact it was being seen by the supposedly "blind" eye. He took great delight in demonstrating this to his students, whenever a suitable patient was in hospital, and he would use it to convince the patient also that he or she could see perfectly with the affected eye.

I should also mention Dr. Russel's famous "red medicine," a weak mixture of bromides and phenobarbital tinted a brilliant cherry red (occasionally the colour was changed to an equally brilliant green), which was like magic in his hands. Bromides are out of date, in these high days of the relaxing drugs — but I do not think I am betraying a trade secret when I tell you that whenever Dr. Penfield has a particularly difficult nervous case he still prescribes that red mixture, which seems to carry with it some of Dr. Russel's old magic.

I have tried in these words to give you a glimpse of Colin Russel, and his distinctive contribution to Canadian neurology. It is difficult to sum it up in a few words, though it was well expressed in a letter I received some weeks ago from Sir Gordon Holmes. He spoke of his long association with Colin Russel and said in part, "My impression of his professional work is that it was distinguished by careful observation and a clear insight into the problems that confronted him. I feel that he brought back to Canada the healthiest features of clinical neurology in England."

This is a correct statement as far as it goes, but is not a man's personality his most distinctive contribution? Although he has left us, Colin Russel's influence continues through those who worked with him and learned from him, and through the tradition of the institution which he helped to shape. His rich and lovable personality forms part of the invisible fabric of this Institute.

BIBLIOGRAPHY

1. TROTT, H. W.: Campus shadows, Crosset & Williams Co., Hemlock, N.Y., 1944.

PUBLICATIONS OF DR. COLIN K. RUSSEL

RUSSEL, C. K.: Leukocytosis and typhoidal perforation, *Boston M. & S. J.*, **144**: 374, 1901.
—Some variations from the type in pulmonary disease, *Montreal M. J.*, **31**: 280, 1902.
—Report on cases of typhoid fever treated in Royal Victoria Hospital during year 1902, *Ibid.*, **32**: 259, 1903.
—Perforation in typhoid fever, *Ibid.*, **32**: 584, 1903.
RUSSEL, C. K. AND HORSLEY, SIR V.: Note on apparent re-representation in the cerebral cortex of the type of sensory representation as it exists in the spinal cord, *Brain*. **29**: 137, 1906.
RUSSEL, C. K.: The visual fields in cases of indirect or incomplete lesions of the optic system, *J. Nerv. & Ment. Dis.*, **33**: 760, 1906.
—Supernumerary cervical ribs and their effects on the brachial plexus and subclavian artery, *M. Rec.*, **71**: 253, 1907.
—Cervical ribs causing pressure on the brachial plexus, *Montreal M. J.*, **36**: 171, 1907.
—A case of partial auditory and visual aphasia with object-blindness due to an abscess of the brain, *Ibid.*, **37**: 517, 1908.
—Tumour of the temporo-sphenoidal lobe and "dreamy states", *Ibid.*, **38**: 75, 1909.
—Acute anterior poliomyelitis with autopsy, *Ibid.*, **38**: 845, 1909.
—A case of destructive lesion of the conus terminalis spinalis, *Ibid.*, **39**: 13, 1910.
—Tabes dorsalis and the "ersatz-theorie", *Ibid.*, **39**: 162, 1910.
—A contribution to the study of acute poliomyelitis based on the observation of thirty-eight recent cases with two autopsies, *Ibid.*, **39**: 456, 1910.
—Tabes dorsalis: the exhaustion theory with experimental evidence, *Canad. M. A. J.*, **2**: 406, 1912.
—On the nature of tabes, Clinic of Dr. Colin K. Russel, Royal Victoria Hospital, page 1879.
—Cerebral arteriosclerosis, *Montreal M. J.*, **38**: 1, 1909.
—Psychogenetic conditions, *Canad. M. A. J.*, **6**: 877, 1916.
—A study of certain psychogenetic conditions among soldiers, *Ibid.*, **7**: 704, 1917.
—Psychogenetic conditions in soldiers, their etiology, treatment and final disposal, *Ibid.*, **8**: 673, 1918.
—War neuroses—some views on diagnosis and treatment, *Arch. Neurol. & Psychiat.*, **1**: 25, 1919.
—The feebleminded in Canada, Canadian National Committee for Mental Hygiene, 1920.
—The syndrome of the brachium conjunctivum and the tractus spinothalamicus, *Arch. Neurol. & Psychiat.*, **25**: 1003, 1931.
RUSSEL, C. K. AND LIROT, S. R.: The technique for staining the tubercle bacillus in the spinal fluid, *Canad. M. A. J.*, **29**: 188, 1933.
CONE, W., RUSSEL, C. AND HARWOOD, R. U.: Lead as a possible cause of multiple sclerosis, *Arch. Neurol. & Psychiat.*, **31**: 236, 1934.
RUSSEL, C. K. AND STAVRAKY, G. W.: The syndrome of the posterior inferior cerebellar artery, *Canad. M. A. J.*, **30**: 358, 1934.
RUSSEL, C. K.: Constantin von Monakow, 1853-1930, *Arch. Neurol. & Psychiat.*, **33**: 1088, 1935.
—Presidential Address, *Tr. Am. Neurol. A.*, **1**: 1935.
RUSSEL, C. K. AND KERSHMAN, J.: Spontaneous subarachnoid hæmorrhage and brain tumour, *Canad. M. A. J.*, **36**: 568, 1937.
RUSSEL, C. K.: The naturé of the war neuroses, *Ibid.*, **41**: 549, 1939.
STEWART, O. W., RUSSEL, C. K. AND CONE, W. V.: Injury to the central nervous system by blast, *Lancet*, **1**: 172, 1941.
ODOM, G., RUSSEL, C. K. AND MCEACHERN, D.: Studies of neuromuscular disorders: The myogram blood cholinesterase and effect of prostigmine in myasthenia gravis and progressive muscular atrophy, *Brain*, **66** (part 1): 1, 1943.

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GENERAL PRACTICE

STRABISMUS—A PÆDIATRIC PROBLEM

ANALYSIS OF 296 CASES*

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STRABISMUS is essentially a pædiatric problem because it arises in childhood. Moreover, if it is not treated in childhood 50% of patients with convergent strabismus become practically blind in one eye, and almost all fail to develop binocular vision.

My purpose in this paper is twofold: to outline the principles of treatment, and to analyze a series of 296 cases so that you may know the results which may be obtained with treatment.

OBJECTIVES IN TREATMENT

There are three fundamental objectives in treatment. These are: (1) A corrected visual acuity of 20/20 in each eye. (2) Straight eyes. (3) Fusion of the two images seen by the eyes.

The last objective is not always attained, but with co-operation from the parents, normal vision in each eye and cosmetically straight eyes can almost always be obtained if the child is seen before the age of six.

PLAN OF TREATMENT

As soon as strabismus is recognized, treatment should be started. Supervision is required until the age of six or seven in most cases. There are four essential steps in treatment.

1. *Correction of Refractive Errors With Glasses*

The ocular fundi should be examined under cycloplegia as soon as strabismus is recognized. I have seen a case of retinoblastoma and two cases of mid-brain tumour in which the presenting complaint was convergent squint.

If there is a refractive error, glasses must be provided for constant use. Some squints are caused by a refractive error alone and in these cases suitable glasses will cure the squint. Children 15 months old will wear glasses quite happily.

2. *Patching of the Good Eye in Cases With Amblyopia*

Whenever there is a constant squint, the deviating eye suppresses in order to avoid double vision, and the vision in that eye fails. It is sometimes necessary to patch these young children for two or three months before normal vision is restored. Moreover, when once the vision is restored to normal it must be checked at regular intervals because the eye frequently resumes the habit of suppression and vision deteriorates again.

3. *Fusion Training or Orthoptics*

The value of orthoptics has often been questioned. All ophthalmologists and pædiatricians are able to point to children with strabismus who have not been helped by orthoptics. From this it must not be argued that orthoptics is of no value. If a long period of orthoptic training proves to be valueless, it is usually because it was not indicated in the first place. In those cases in which it is indicated, it is undoubtedly of great value. Children under the age of five are seldom able to co-operate effectively in this form of treatment.

4. *Operation*

If the foregoing measures fail to straighten the eyes, surgery is indicated. Parents tend to expect that one operation will cure squint just as appendicitis is cured by appendectomy. But there are so many variables which control the position of the eyes that it can never be guaranteed that one operation will cure strabismus. One, two or sometimes three operations may be required. Surgery should be regarded as no more than a part of the over-all plan of treatment.

RESULTS

In the last three years I have seen 296 consecutive cases of strabismus in my private practice.

ANALYSIS OF CASES OF STRABISMUS

	Under age 8	*Over age 8*	*Total*
Convergent strabismus	112	58	170
Divergent strabismus	24	58	82
Ocular muscle palsies	7	37	44
Total			296

The cases have been divided arbitrarily into two groups, those under and those over the age of eight, because treatment of a squint after the age of eight rarely results in a cure. The eyes may be made to appear straight by operation, but vision in one eye often remains defective and binocular vision cannot be expected.

This group of 112 includes both intermittent and constant convergent strabismus cases. Sixty-three or 56% were amblyopic with a corrected vision of less than 20/30 in the squinting eye when first seen. A cure was taken to be vision of 20/30 or better in each eye, straight eyes and

*Read at the Annual Meeting of the Canadian Pædiatric Society, Winnipeg, June 14, 1957.
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CONVERGENT STRABISMUS UNDER THE AGE OF 8 YEARS

Cured without operation	20
Cured with operation	21
Cosmetically straight after operation	16
Still under treatment	29
Failed to continue treatment	26
Total	112

some degree of fusion. Of the 41 cases cured, 20 were cured by spectacles, patching and orthoptics. These were early accommodative cases and it is in these cases that the best results are obtained.

Thirty-seven cases required operation to straighten the eyes. Of these, 21 cases obtained fusion and in 16 cases the eyes appeared straight but were unable to fuse. Twenty-nine are still under treatment. Many of these are straight as a result of operation but fusion has not developed. It is hoped that periodic patching and orthoptic training may help develop fusion, but it is probable that less than half the number will gain a normal binocular relationship.

CONVERGENT STRABISMUS OVER THE AGE OF 8 YEARS

Operation giving fusion	5
Operation giving a cosmetic result	25
Operation refused	12
Operation not advised	16
Total	58

Of this group of 58 patients 31 or 54% were amblyopic and had vision of less than 20/30 in one eye. This defective vision could have been avoided by adequate treatment at the onset of the squint. Most of the 16 patients on whom operation was not advised were elderly adults.

DIVERGENT STRABISMUS UNDER THE AGE OF 8 YEARS

Cured by operation	10
Still under treatment	9
Failed to continue treatment	5
Total	24

Twenty-four children were seen with divergent strabismus. The majority of these were intermittent, one eye wandering outwards when the child gazed into the distance or was tired. An interesting feature of this type of strabismus is that amblyopia seldom occurs. This is because of the intermittent nature of the deviation. Only two of this group of 24 had amblyopia.

It is only during the last decade that divergent strabismus has been treated by operation. Yet more satisfactory results are obtained in divergent than convergent strabismus. This group included many adults.

DIVERGENT STRABISMUS OVER THE AGE OF 8 YEARS

Cured by operation	21
Under treatment	3
Operation refused	17
No operation advised	17
Total	58

OCULAR MUSCLE PALSIES

Forty-four patients with paralyses of ocular muscles were seen, but only seven of these were children under the age of eight.

The operative treatment of these cases is a relatively new development. The work of Lyle and Fink and others has done much to improve and popularize surgery to correct deviations resulting from palsies of extraocular muscles.

AMBLYOPIA

In most cases of squint there is still too long an interval between onset and treatment. Parents often say they were told to wait until the child was older because he might outgrow the squint.

There is actually some truth in this statement. A blind eye always tends to diverge. Therefore, as soon as a squinting convergent eye has learned to suppress and has become amblyopic it begins to diverge and the angle of squint becomes smaller. Thus it is true that nature often straightens a squinting eye but the price is loss of sight.

Fifty-four per cent of the patients with convergent strabismus over the age of eight were condemned to lifelong amblyopia in one eye as a result of inadequate treatment at the onset of the squint.

A patient recently attended our department with a suspected melanoma of choroid in his only seeing eye. The other eye is amblyopic and his vision is only 20/200. If the only seeing eye is removed, this patient will be blind. A case like this emphasizes the importance of the treatment of amblyopia in childhood.

FEAR OF SURGERY

Fear that surgery may result in loss of sight is the most frequent cause of refusal to accept operation. In reality danger to sight is negligible because in a squint operation the eye muscles only are subjected to surgery.

The only complication which may occur is that the squint may be slightly over-corrected and a convergent eye made to diverge or a divergent eye to converge. These have to be put right by a second operation.

Many parents fear the psychic trauma of an eye operation. This is a grossly over-rated danger. The stay in hospital is not more than two to three days and the postoperative pain is not severe. The unkindness of other children and the child's own reflection in a mirror cause much more psychic trauma than the operation.

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In 46 cases in this series operation was advised but not accepted. In 29 of these the operation was merely for cosmetic reasons, but in 17 children operation was advised in order to straighten the eyes so that binocular vision could develop. The parents' refusal to allow operation means that most of these children will lose the sight of one eye and all will have the psychological burden of an unsightly deformity.

In conclusion I wish to emphasize three important points.

1. In order to save sight, a child should be referred to an ophthalmologist for treatment as soon as a strabismus is noticed.

2. When patching has restored the vision of an amblyopic eye to normal, the child should be seen at regular intervals so that any return of amblyopia may be detected and treated.

3. Operation should not be delayed once it is apparent that other forms of treatment will not effect a cure.

REFERENCES

1. COOPER, E. L.: *Am. J. Ophth.*, 40: 883, 1955.
2. FINK, W. H.: Surgery of the oblique muscles of the eye, C. V. Mosby Company, St. Louis, Mo., 1951.
3. LYLE, T. K. AND FOLEY, J.: *Brit. J. Ophth.*, 41: 129, 1957.
4. LYLE, T. K. AND CROSS, A. G.: *Ibid.*, 35: 511, 1951.
5. SCOBEE, R. G.: The oculorotary muscles, C. V. Mosby Company, St. Louis, Mo., 1952.

SCIENTIFIC ASSEMBLY AT WINNIPEG

THE COLLEGE OF GENERAL Practice of Canada announces that it will hold its 1958 Convention at Winnipeg, April 14-16. Speakers on the scientific program come from various centres in Canada and the U.S.A. They include Dr. J. A. Emile Simard of Quebec, Dr. Roméo Boucher of Montreal, Dr. J. Portnuff of Montreal, Dr. Marion Hilliard of Toronto, Dr. John D. Keith of Toronto, Dr. John F. McCreary of Vancouver, Dr. R. C. Dickson of Halifax, Dr. Blake Watson of Los Angeles and Dr. W. A. Lange of Detroit. The Dean of Divinity, Trinity College, University of Toronto, Dr. Charles Feilding, will discuss medicine and religion, and the general director of the Canadian Mental Health Association, Dr. J. D. M. Griffin, will participate in convention sessions. All addresses will be available in printed form in English and French, and three round-table discussions will be included in the program.

All standing committees of the College will hold meetings in the Royal Alexandra Hotel between 8:30 and 10 p.m. Monday night, April 14. Registration begins on Sunday night at 7 p.m. and the Credentials Committee will also meet on Sunday night.

Approximately 100 exhibits have been arranged for the convention. The health examination for attending physicians will again be provided, with more complete examinations; this is under the joint direction of Dr. John Z. Gillies of Toronto and Dr. R. A. Jacques of St. Boniface, Manitoba.

The Central Program Committee for the 1958 convention has Dr. Peter A. Kinsey of Toronto as chairman; the chairman of the Committee for Arrangements in Winnipeg is Dr. A. J. Winestock, and housing is under the direction of Dr. A. J. Henderson of St. James, Manitoba.

ASSESSMENT OF STUDY RECORDS

A VERY HIGH percentage of the active members of the College have reported postgraduate studies for the first two years of their membership (June 1954-June 1956) which have earned for them recommendations from the Credentials Committees for another two-year period of membership.

Developing smoothly functioning machinery at the central office to deal with these regulations has been a new experience. Little guidance has been possible, since no other organization has such standards for continuing membership. A few observations, based on experiences to date, may be made:

1. A few members have not sent in their records of studies—and this includes several who have given very valuable service to the College. Where this occurs, continuing membership in the College cannot be granted by the Credentials Committees.

2. Most members have recorded studies on the combined membership and record-study card. A few have listed them separately and more fully.

3. A few members are short of the required studies. Interestingly enough, there is a higher percentage in this category in the larger cities than in the smaller places.

4. Members who have given much time to their medical associations, to Trans-Canada Medical Plans, to welfare plans, etc., should record these activities on the reporting cards.

5. It is much easier to report studies annually when renewing membership than to wait until the last moment to try to recall educational activities of two or even three years earlier. It is a new experience for busy general practitioners to report the scientific meetings they have attended, but it is much easier to do this each year.

6. Associate members are required to follow postgraduate study requirements. They also will find it easier to report these annually. Such reports are kept in each member's file. It is hoped that associate members will apply for active membership as soon as they can qualify. There is a five-year time limit to associate membership.

PHYSICIANS IN PARLIAMENT

CANADA'S 23rd Parliament, like the previous one, has eight physicians among its members. Two of these, both from Toronto ridings, are College members—Dr. Stanley Hajdasz, Liberal, and Dr. John Kucherepa, Conservative. The other six doctor members of Parliament are: Dr. Pierre Gauthier of Portneuf, Dr. W. H. McMillan of Welland and Dr. Raoul Poulin of Beauce, all re-elected; Dr. Percy Vivian of Durham, Dr. P. B. Rynard of Orillia and Dr. Rodolphe Leduc of Maniwaki. The last three, like Drs. Hajdasz and Kucherepa, have taken office for the first time.

Provincial parliaments of all provinces except Saskatchewan and British Columbia have one or more physicians in their membership. The Quebec legislature has ten doctors, including three cabinet ministers; Nova Scotia has seven doctor members. Five College members are among the 26 doctors in provincial parliaments: Dr. Henry Reardon, Halifax; Dr. J. D. Ross, Edmonton; Dr. J. Antoine Raymond, Témiscouata, Que.; Dr. Lloyd G. Dewar, O'Leary, P.E.I.; Dr. Matthew B. Dymond, Port Perry, Ont. Dr. Dewar was a member of the College Board of Representatives last year. Dr. Dymond was recently given a cabinet post in the Ontario Government.

The Canadian Senate similarly has representation from the field of medicine with six physicians.

POSTGRADUATE COURSES FOR GENERAL PHYSICIANS

Title of course	*Location*	*Dates*	*Fees*
CANADA			
Second Scientific Convention, College of General Practice of Canada	Royal Alexandra Hotel, Winnipeg, Manitoba	April 14-16, 1958	
ONTARIO			
Toronto Chapter Clinic Day	Northwestern Hospital	November 20, 1957	
General Practitioner's Day, University of Western Ontario	Dept. of Pædiatrics, University of Western Ontario, London	October 23, 1957	
Refresher Course	Medical Alumni, University of Toronto	October 23-25, 1957	
Clinic Day	St. Joseph's Hospital, Toronto	October 10, 1957	
Canadian Society for the Study of Fertility	Y.M.C.A.-Y.W.C.A., London	November 8, 9, 1957	
Refresher Course in Public Health and Preventive Medicine	University of Toronto, School of Hygiene	February 10-12, 1958 Feb. 12	3 days $35 $15.00
Section of General Practice Clinic Day	Hamilton	April 16, 1958	
Fracture Course	Niagara Falls Medical Group	May 7-9, 1958	
QUEBEC			
Postgraduate Course for General Practitioners	Chicoutimi	October 21-26, 1957	
Refresher Course for G.P.'s	Royal Victoria Hospital, Montreal	Nov. 11-16, 1957	$50.00
Postgraduate Course in Pædiatrics	Sainte-Justine Hospital, Montreal	One week in October	$10.00
NOVA SCOTIA			
Annual Refresher Course	Faculty of Medicine, Dalhousie University, Halifax	October 7-11, 1957	
BAHAMAS			
4th Bahamas Medical Conference	Fort Montagu Beach Hotel, Nassau, Bahamas B. L. Frank, M.D., 1290 Pine Ave. W., Montreal	December 1-15, 1957	
U.S.A.			
General Medicine	Chicago Medical Society,	November 4-8, 1957	$75.00
Obstetrics, Gynecology and Pediatrics	86 East Randolph Street, Chicago, Ill.	Nov. 11-15, 1957	$75.00
Annual Fall Postgraduate Clinic, Michigan Academy of General Practice	Sheraton-Cadillac Hotel, Detroit, Mich.	November 6-7, 1957	
National Assembly, American Academy of General Practice	Dallas, Texas	March 24-27, 1958	

Cook County Graduate School of Medicine (707 South Wood St., Chicago 12, Ill.) and the New York Polyclinic Medical School and Hospital (345 W. 50th St., New York) have a wide range of concentrated courses.

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MEDICAL MEETINGS

MEDICAL CONGRESS IN RUMANIA

The first medical congress of the Rumanian Peoples' Republic was held in Bucharest from May 5 to 11, 1957. The occasion was the 100th anniversary of the foundation of the medical school in Bucharest. A few invitations were sent to each of many countries, both in the West and behind the Iron Curtain. There were about 100 foreign delegates from countries ranging from China to Uruguay. In addition the congress was attended by many Rumanian doctors.

The proceedings were opened by formal greetings to the foreign delegates and by a résumé of medical achievements in Rumania, given by the Minister of Health and prominent members of the Rumanian Academy. One representative of each visiting country was then asked to give a short address. In most instances this took the form of greetings from members of the medical profession of that country to members of the medical profession in Rumania. Thereafter the various sections were kept occupied for five days with their deliberations. There were numerous papers and visits to hospitals and institutions in Bucharest. Four topics had been chosen for discussion and the delegates were divided into groups accordingly. The subjects were neurophysiology, rheumatology, microbiology and epilepsy. Each of the four meetings was held simultaneously in different amphitheatres. There were six official languages of the congress and simultaneous translations through earphones were available.

The section on epilepsy was opened by Prof. A. Kreindler, a member of the Rumanian Academy of Sciences and Professor of Neurology. He gave an extensive review of recent work and current concepts of epilepsy in Rumania. In general, his conclusions were very similar to those accepted in this country. He shows a great interest in reflex epilepsy with particular reference to reflex epilepsy induced by conditioned reflexes. He and his colleagues have been able to condition dogs so that they have generalized or focal seizures induced by the usual conditioning stimuli such as the ringing of a bell or the shining of a light. He is endeavouring to use this technique to unravel the complicated problem of the "level of function" of the conditioned reflex in the central nervous system. He points out that it helps explain some difficult manifestations of epilepsy, such as the problem of trigger factors for the individual attacks. Methods of treatment were discussed and are similar to those used in this country. He makes the observation that 40% of all the patients he sees suffering from focal epilepsy have no apparent cause for their attacks. He has made a study of the biochemical differences between people who have "psychic disturbances" and epilepsy and epileptics who do not have such disturbances. He makes the interesting observation that an increase in blood glycogen has been observed in the first group, but it would seem that these results need further confirmation.

Thereafter a number of short papers were given. Of particular interest from the local group was the paper by Dr. N. Marcovitici, who had studied the effect of cortisone on fibrous tissue formation after cerebral trauma. His work was ably performed and well presented. It confirms some fairly recent work in this country—the published reports of which were not apparently available to Dr. Marcovitici at the time of his investigation. Professor Kreindler *et al.* presented their unusual experiences of epilepsy from cerebral paragonimiasis. Dr. V. Ionasescu presented some interesting observations on intramuscular mescaline as an activating substance in temporal lobe seizures. In both his cases some electroencephalographic temporal lobe activity had been induced. A number of papers reported the local experiences with various strains of the Coxsackie virus and poliomyelitis and encephalitis virus using tissue culture techniques. Of the foreign delegates, among the more interesting papers was that by Dr. Denis Williams of London who gave evidence for the thalamic origin of the "spike and wave" complex in children with petit mal, and Dr. Z. Servit of Czechoslovakia who discussed the ability of organisms to convulse at various levels of the phylogenetic scale.

Visits were made to the Pavlov Institute, the neurological hospital and the children's hospital. The Pavlov Institute is the chief centre of neurological research. As the name might suggest, a large amount of its effort is concerned with various aspects of conditioned reflexes but, in addition, there is an extensive neuropathological laboratory and other smaller departments, such as the department of electroencephalography. The hospitals are also centres of investigational work. The children's hospital is a new building and very well equipped. The standard of medical care appeared to be good.

In between the scientific sessions the delegates were kept very busy with a most admirable program of entertainment. The concert put on by the orchestra of doctors in Bucharest was particularly enjoyable; but it is invidious to mention that and not a most polished and magnificently produced and costumed ballet based on a Rumanian legend, an astonishingly charming and realistic puppet show and some fine Rumanian traditional dancing. When any free time was available, there were always people apparently willing and anxious to show one the local points of interest, of which there are very many.

During the whole of this time, the arrangements for the delegates' wellbeing were excellent and set a standard of kindness and hospitality that is extremely difficult to match. At the airport, on the day preceding the meeting, each plane was met by Professor Nicolau, the chairman of the congress, and other prominent medical members of the Academy. In each delegate's hotel suite or room were found bound volumes containing copies of all the papers to be presented to the congress in all

the official languages of the congress—Rumanian, English, French, Spanish, Italian and Russian. In order that the time spent in Rumania would involve no expense at all, meal tickets were provided, as was $50 worth of local currency for incidentals and presents to take home. An interpreter, in most cases a physician, was allotted to each person and was available to him at any time for the duration of his stay. Several cars and chauffeurs belonging to the Academy were made available for transportation within the city.

When the scientific meetings were over, arrangements were made for those who did not wish to leave immediately to go on a tour, either to the mountains or to the Danube. The Danube party was taken by train to the town of Galatz, where a paddle steamer was waiting for them. The next four days were spent exploring the delta of the Danube down as far as the Black Sea. In this pleasantly relaxed environment the opportunities for discussion with doctors of far-away countries were ideal. A combination of English and French was sufficient for most needs, but if, for instance, one wished to discuss ideology with a representative from North Korea, an interpreter was always available.

On returning to Canada one was left with a host of impressions of this visit behind the Iron Curtain.

In the field of medicine the pervading feeling is one of enthusiasm and determination. Every effort is being made to have Rumanian methods compare favourably with any part of the world. This applies not only to the routine care of the sick but also to investigative work. But it is apparent that they are hampered in this ambition by a lack of material wealth. This makes itself felt in many ways. The most obvious is the shortage of equipment. The more specialized kinds of medical journals—so essential to the research worker—are few and far between. Many of them are available in the central library, but individuals and groups such as hospital staffs usually find it impossible to obtain them for themselves. More subtle and probably more serious is the lack of opportunity for younger men to travel to centres in other countries. In spite of these handicaps, medicine in Rumania would appear to be tackling aggressively the problem of raising its standards so that they might compare favourably with those of any other country.

It is impossible for a Westerner to visit Rumania and not to be very much aware of the prevailing political system and ideology. At first one is shocked by the rigid censorship of information passed on to the public. It seems that all the newspapers in Bucharest—and they appear under several different names—are published in the same building and contain essentially the same news and editorial point of view. There are many bookshops in Bucharest, but 50% of the books on view are ideological works by Marx, Lenin and other communist leaders. The public libraries have a large section devoted to the same ideological treatises. Other views are not tolerated by the authorities and are not allowed in the country. I am informed, for instance, that copies of *Life*, *Time* or *The New Yorker* will be confiscated. And this would also apply to provocative works of fiction, such as George Orwell's *Animal Farm* or *1984*. But when one begins to understand the problems of the country a little better, it becomes apparent that a great effort is being made to convert a hitherto primarily agricultural and backward country into a modern one. For this change to come about within a reasonable time an authoritarian discipline is useful. It is the philosophy of the end justifying the means. It remains intolerable but it becomes understandable.

But the largest impression by far is of the friendliness of the individuals I met. They seemed genuinely pleased to meet a Canadian and to discuss problems of mutual interest—medical and otherwise. It has been said so often that it has become almost banal; but I like to think that friendships formed in this way help to dispel some of the distrust and misunderstanding in the world today. I know that the Rumanian medical profession by holding such an admirable meeting has fostered a great deal of interest and goodwill among their guests. They are to be congratulated.

J. STOBO PRICHARD,
Toronto.

CANADIAN ASSOCIATION OF PHYSICAL MEDICINE AND REHABILITATION

At the annual general business meeting of the Canadian Association of Physical Medicine and Rehabilitation, the following officers were elected. President: Dr. Gustave Gingras; Vice President: Dr. John S. Crawford; Secretary: Dr. Maurice Mongeau; Treasurer: Dr. Talmadge E. Hunt; Chairman, Exhibits and Recreation Committee: Dr. Maurice Delâge. The sixth annual meeting of the Association will be held in Quebec City on June 12, 13 and 14, 1958. Information about the Association may be obtained from the office of the Secretary, Dr. M. Mongeau, 6265 Hudson Road, Montreal, Que.

PHARMACOLOGICAL SOCIETY OF CANADA

The Pharmacological Society of Canada will hold its second annual meeting at Ottawa on October 9, 1957. The Society was invited to meet there by Assistant Dean Lussier of the University of Ottawa and Dr. Clare A. Morrell, Director of the Food and Drug Directorate. The meeting will take place on the afternoon and evening of October 9, and consist of a tour of the Food and Drug Laboratories, a symposium under the chairmanship of Dr. Mark Nickerson, a Pharmacology Dinner and a business meeting. The symposium will be on

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"The role of pharmacologists in teaching therapeutics", and the panel will consist of Dr. John G. Aldous, Dalhousie University, Dr. K. J. R. Wightman, University of Toronto, and Dr. Mark Nickerson, University of Manitoba. At the Pharmacology Dinner the speaker will be Dr. Maurice F. Murnaghan, whose topic will be "Additional courses in pharmacology".

AMERICAN COLLEGE OF SURGEONS

All members of the medical profession are invited to attend any of the following 1958 Sectional Meetings of the American College of Surgeons being held in conveniently located cities of the United States, with one supplementary meeting in Sweden.

Meeting cities and dates are:
Dallas, Texas, January 9-11.
Jackson, Mississippi, January 16-18.
New York City, March 3-6.
Salt Lake City, Utah, March 17-19.
Des Moines, Iowa, March 27-29.
Stockholm, Sweden, July 2-7.
44th annual Clinical Congress, Chicago, October 6-10.

All Sectional Meetings draw on surgeons of outstanding ability to discuss problems encountered in daily practice, and to disseminate information about new techniques. Usefulness is the keynote of all College programs, which are planned by local committees answering the needs and wishes of doctors within the meeting area. Panels, symposia, papers, medical motion pictures, and question-and-answer periods characterize the meetings.

Two new features are scheduled for each Sectional Meeting this year: a fellowship luncheon, at which a panel of College officials will answer questions about the entire program of College activities, and, in turn, pose questions to the audience; a social, rather than scientific, dinner meeting, to which program participants, visiting surgeons, wives and other guests are cordially invited for an informal and pleasant evening of entertainment.

SEVENTH INTERNATIONAL CANCER CONGRESS, LONDON 1958

Those planning to attend the 7th International Cancer Congress, which will take place at the Royal Festival Hall, London, July 6-12, 1958, are reminded that enrolment forms must be received at the Congress Office (45 Lincoln's Inn Fields, London, W.C. 2) *by January 1, 1958*, if a late fee is not to be incurred. Registration forms may be obtained from the Secretary-General at that address.

PUBLIC HEALTH

INFLUENZA

The influenza pandemic is decreasing throughout Asia, as well as in Egypt and in East and South Africa. It continues, however, to spread to new countries or territories in West Africa (Sierra Leone and Ghana, for example), in addition to South and Central America; its appearance has been reported in some areas of Brazil, which had not been affected before, as well as in El Salvador. In North America and Europe the spread of the disease is considerably slower. Even in the very few countries where the disease has affected up to 50% of the population, complications have remained exceptional and the mortality has been very low.

The situation in Canada is as follows:

In Quebec, Dr. A. R. Foley, Provincial Epidemiologist, reports the occurrence of influenza-like disease in the following localities: Three Rivers: The outbreak previously reported at the Seminary has now subsided. At another school 75% of the pupils are said to be absent with a mild influenza-like disease of three to four days' duration. Rouyn: An incidence of influenza-like disease up to 25% is reported in the schools. In the pupils of a Classical School, aged 12 to 18 years, the incidence is said to have reached 40%. Hull: A mild influenza-like disease is reported in a number of schools, the incidence being from 10 to 20%; a number of cases have occurred in the general population. The isolation of Asian strain influenza has been made from a number of passengers from the ships *Ivernia* and *Homeric* who were hospitalized at Quebec City and Montreal.

In Ontario the occurrence of a mild influenza-like disease of short duration has been reported by Dr. W. G. Brown, Chief Medical Officer of Health, from a number of localities, including Sudbury, Mattawa, North Bay, Sault Ste. Marie, Sturgeon Falls, Prescott and Ottawa. Laboratory identification is proceeding. In Ottawa, the identification of Asian strain influenza virus has been made in a specimen from a Chinese patient who arrived by air direct from Hong Kong, as well as from two other patients in the Ottawa area.

In Alberta, the occurrence of some 65 cases of an influenza-like disease of short duration in a military unit is reported in Calgary. Laboratory specimens are being examined by the Laboratory of Hygiene, Ottawa. Asian strain influenza virus has been verified in two Boy Scouts and an Air Cadet who were reported ill on arrival by air from Europe.

In Saskatchewan, Dr. Percy Moore, Director of Indian Health Services, has reported an outbreak of 130 cases of influenza-like disease in a residential school population of 300 at Lebret, near Fort Qu'Appelle.

Word has been received that commercial supplies of influenza vaccine (Asian strain) may be obtained by physicians through the usual pharmaceutical outlets.

LETTERS TO THE EDITOR

NATIONAL HEALTH INSURANCE

To the Editor:

The attached item published in the British press on August 31, 1957, might prove interesting to your readers in view of the "politicking" in our country for a national health scheme.

It should be remembered when interpreting these charges that £1 is worth $2.60 of our dollars but that wages in Britain are substantially lower than in Canada.

A. L. HUDSON, M.D.

National Insurance and National Health Service

NEW COMBINED CONTRIBUTIONS FROM 2nd SEPTEMBER

WHY YOU HAVE TO PAY MORE

"There's a widespread belief that the whole cost of the National Health Service is met by weekly contributions. This is not so.

"Since 1949, the cost of the National Health Service has risen from about £450,000,000 to about £690,000,000. The total amount transferred each year from the weekly contributions has remained unchanged at £40,000,000.

Under the National Health Service Contributions Act 1957

"The N.H.S. contribution—until now between 6d. and 10d. per week—is to be raised to between 1/- and 1/8d. per week. For employed persons part of the increase will be paid by the employer. The increased contribution will yield £80,000,000 a year—enough to cover about one-ninth of the cost of the Service.

"Hitherto, the National Health Service contribution has been included in the National Insurance contribution. Now there is to be a *separate* N.H.S. contribution.

"For economy and convenience, however, both contributions will be paid together, combined in a single stamp."

1 Roxborough St. E.,
Toronto, Ont.,
September 5, 1957.

ROYAL COLLEGE CERTIFICATION

To the Editor:

In the past year the council of The Royal College of Physicians and Surgeons of Canada have been giving consideration to the question of discontinuing the Certification examination in a few approved specialties. The study of this matter has taken place in collaboration with the appropriate specialty committees of the College and in some instances with the national societies. The group of specialties so studied to the present time has been small.

At the last meeting of the Council of The Royal College of Physicians and Surgeons of Canada there was approved a resolution stating that the Certification examination in Neurology and in Neurosurgery would be discontinued as of 1962. In that year and thereafter Certification in Neurology will be granted by this College on the basis of success at the Fellowship examination in Medicine as modified for Neurology; similarly Certification in Neurosurgery will be granted on the basis of success at the Fellowship examination in Surgery as modified for Neurosurgery. JAMES H. GRAHAM, F.R.C.P.[C.], Secretary.

150 Metcalfe St.,
Ottawa, Ont.,
August 14, 1957.

MEDICAL ETIQUETTE

To the Editor:

I would like to congratulate you on your editorial "Medical Etiquette". You are so right when you say that the "time to inculcate medical etiquette is at the undergraduate stage *and by example*—not by lecture"!

We are practising intolerance in the fullest sense when we deny the privilege of our hospitals to all fully qualified physicians in good standing. How can a medical student acquire medical manners and tolerance, when most of his teachers do not consider that ethics includes them as well! The British solicitor could be quite right in making the same statement about Canadian chiefs of staff.

P. BEREGOFF-GILLOW, M.D.

915 Medical Arts Bldg.,
Montreal, Que.,
August 29, 1957.

THE LONDON LETTER

(From our own correspondent)

POLIOMYELITIS VACCINE

The Government has at last been stirred into action over the pathetically inadequate supplies of poliomyelitis vaccine that our own laboratories have been able to produce. The visit of the two experts to Canada to see whether the Connaught Laboratories can make good our deficiencies has now been followed by the announcement that two of the Ministry of Health's medical officers are to go to Paris to discuss the offer of a supply of vaccine from the Pasteur Institute there. Meanwhile the number of notified cases rises weekly. At the moment they are running just a little lower than

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the highest level reached since 1948. The whole episode is a pathetic—one only hopes that by the end of autumn "tragic" will not be the more appropriate description—example of political bungling. To what extent the blame should be apportioned among the Minister of Health, his technical advisers, and the manufacturers of the vaccine it is impossible to say on the available evidence. All that the public—and many doctors—are concerned about is that we seem to be the only country in the world that is unable to obtain adequate supplies of the vaccine.

INFLUENZA

Asian influenza begins to vie with poliomyelitis vaccine as a topic of public interest. It has now reached this country—so far in a mild form and involving principally closed communities. The highest incidence, curiously enough, appears to be among United States Air Force personnel, and the public have been intrigued by the reports that wholesale inoculation of all United States Air Force personnel is well under way. So far as the natives of these Islands are concerned, what has happened is that the Wright-Fleming Institute has produced an experimental batch of vaccine against the New Asian strain, and this is now going into production. The Ministry of Health is forestalling criticism of inadequate supplies by pointing out that our past experience of influenza vaccine has not been particularly happy, results in past winters having shown that such vaccines have usually not given more than 30 to 40% protection.

CHILDREN IN HOSPITAL

Insistence upon the importance of an informal and almost domestic atmosphere in a children's hospital is the keynote of a memorandum on children's hospitals published by the British Pædiatric Association. For infants and toddlers it is recommended that there should be facilities for admission of child and mother, with the mother sleeping in the same room as the child and helping in his care. Whenever possible, all the children's beds in a hospital should be gathered in a single ward unit, or series of units, with a designated consultant pædiatrician in charge of general ward arrangements The ward unit should contain about 20 and not more than 24 cots or beds, and should be arranged in small sections for infants and children of different age-groups. The special difficulties of adolescence should be recognized by the provision of suitable separate accommodation. Stress is laid upon the importance of the permanent and senior nursing staff being trained in the nursing of children, and they must be adequate in temperament and proficient to meet the special requirements of children and their parents. Teaching and large non-teaching hospitals should have a training school for children's nurses to combine the stimulus of a training-school and a source of children's trained nurses and staff nurses for the hospitals of the region.

VITAMINS FOR CHILDREN

Now that margarine, national dried milk and infant cereals are all "fortified" with vitamins A and D, and at the same time mothers are being exhorted by the advertisement pages of the national press to supplement their children's diets with expensive, and often concentrated, forms of these two vitamins, it is scarcely surprising that even Mother Nature is finding it difficult to protect the human offspring of today from premature calcification. The danger is at last being realized, and in its recently published report the joint subcommittee on welfare foods, appointed by the Ministry of Health and the Department of Health for Scotland, has recommended that the vitamin D content of national dried milk be reduced from the present minimal content of 280 i.u. per oz. to 90-100 i.u. per oz. of powder (average), and that for infant cereals be reduced from the present level of "up to 1000 i.u. per oz., minimum" to 300 i.u. per oz. of dried cereal (average). At the same time it is recommended that the D content of national cod-liver oil be reduced from 200 i.u. per g. (minimum) to 100 i.u. per g. (average).

More controversial is the majority recommendation of the committee that "there is no need to provide welfare orange juice for children over two because scurvy is virtually non-existent after that age". Two members have recorded their dissent from this recommendation. They consider that "the provision of orange juice is valuable as a token of its nutritional importance" and hold that "any measure towards an improved intake of vitamin C by children aged two to five years is to be supported, as it is in the years of rapid growth that the needs for nutrients in general are no doubt greatest". WILLIAM A. R. THOMSON

London, September 1957

ABSTRACTS *from current literature*

MEDICINE

Pulmonary Tuberculosis and Diabetes Mellitus.
M. T. WARWICK: *Quart. J. Med.*, 26: 31, 1957.

Study of a large series of diabetic patients showed that pulmonary tuberculosis was present in 1.8% as compared with 0.49% of the general population. Pulmonary tuberculosis was more frequent among diabetic patients whose diabetes was poorly controlled. The advent of the antituberculous drugs has markedly improved the prognosis of pulmonary tuberculosis in diabetic patients; prior to 1950 25% of such patients died within three to seven years of the onset of the tuberculosis. No death has yet occurred among the patients treated with antituberculous drugs.

This study stresses the importance of early diagnosis of tuberculosis in diabetics, the need for good

control of the diabetes in such patients, and the great value of the antituberculous drugs in treatment. Unlike previous investigators, the author could find no typical x-ray pattern for pulmonary tuberculosis in diabetics. NORMAN S. SKINNER

The Cardiorespiratory Syndrome of Obesity.
G. A. LILLINGTON *et al.*: *Dis. Chest*, 32: 1, 1957.

Marked obesity may be associated with alveolar hypoventilation, arterial hypoxæmia, hypercapnia and secondary polycythæmia in the absence of primary pulmonary or cardiac disease. Pulmonary hypertension and right cardiac failure may develop secondarily. Appropriate loss of weight is accompanied by reversal of these complications. In patients with primary pulmonary or cardiac disease, obesity aggravates the dysfunction, and loss of weight may produce considerable clinical improvement.

The cases of eight obese patients studied at the Mayo Clinic are reported. In four patients, obesity and secondary polycythæmia were present without intrinsic pulmonary disease. In three patients with pulmonary disease, obesity was thought to have played a significant role in the development of hypoxæmia and secondary polycythæmia. One patient had no polycythæmia but tests of pulmonary function suggested that he manifested the early stages of ventilatory impairment of obesity.

The writers suggest that the mechanical effect of obesity in increasing the work of breathing is the primary factor in the genesis of the alveolar hypoventilation which appears to be the significant abnormality. S. J. SHANE

Epidemic Bronchiolitis of Infants, Nova Scotia, 1956.
E. ROSS *et al.*: *Postgrad. Med.*, 22: 87, 1957.

During May, June and July 1956 an epidemic of respiratory disease occurred among children in Halifax, Nova Scotia. The disease was most severe in infants less than two years of age. In the month of June alone, some 160 patients with pneumonia were cared for at the Children's Hospital, more than twice the number admitted during the same month in previous years. Elsewhere in Nova Scotia, at New Glasgow, 15 patients were admitted to hospital and two died. At New Waterford, 11 children whose cases were typical of the condition were hospitalized and two died. Likewise, Glace Bay and Sydney were affected, and from the reports of practising physicians in the area it appeared that a sizable epidemic was attacking the infant population.

Difficulty in breathing was the main reason for admission to hospital. The onset of illness was sometimes sudden and ushered in by dyspnœa. In other cases there was a prodromal phase of one to seven days with irritability, cough and nasal discharge. Fever was a prodromal feature in more than half the cases. Vomiting and diarrhœa were less common. All the children were x-rayed on admission to hospital. Emphysema with depressed diaphragm, more horizontal rib shadows and radiolucent lung fields indicated that the chest was fixed in extreme inspiration. Small areas of increased density, either atelectasis or infiltration, were common but there was no lobar or widespread consolidation.

All the children were treated with antibiotics, and the gravely ill received as many as three types at one time—most commonly penicillin, streptomycin and chloramphenicol. Many infants had been on antibiotic therapy from the onset of the respiratory symptoms several days before the increasing difficulty in breathing demanded hospitalization. There did not appear to be a difference in the severity or duration of the disease between those treated early and those started on therapy at a later date. Nor could any difference be detected in response to the different antibiotics or their dosages.

Postmortem examinations were performed on three children who died of the disease. On gross examination, organs other than the lungs appeared normal. The lungs were emphysematous with patchy dark areas and no excess of pleural fluid. Histologic examination of organs other than the lungs showed congestive changes only. In the lungs there were areas of atelectasis alternating with areas of emphysema. The bronchi and bronchioles were surrounded by mononuclear infiltration which extended into the interalveolar tissue. The bronchioles in two cases were filled with exudate containing neutrophils and mononuclear cells. Most of the alveoli were clear except the affected bronchioles, where they also contained inflammatory exudate. Inclusion bodies were not found. Interstitial pneumonia was present in one case and bronchiolitis was present in the other two.

The etiology of the epidemic observed is hard to determine. Since every child was treated with antibiotics, the failure of these agents to exert a specific or dramatic effect on the course of the illness suggests that the disease was probably viral in origin. Influenza virus could not be recovered from nasopharyngeal exudate obtained by aspiration from acutely ill children. There was no evidence to suggest that epidemic influenza or other forms of acute respiratory disease were prevalent among the adult population, either in any area where these cases occurred or among family contacts.

Four viruses cytopathogenic to HeLa cell tissue cultures were isolated. Three of these agents appear to be identical; one was recovered from nasopharyngeal secretion and the other two from fæces. The fourth agent was also obtained from fæces but appeared to behave differently in HeLa cell cultures. All were propagated serially without difficulty.

Attempts are now being made to identify the agents isolated and determine their etiologic relationship to their associated clinical entities.

S. J. SHANE

Bronchospasm in Bronchography.
T. H. HEWETT *et al.*: *J. Thoracic Surg.*, 33: 609, 1957.

The phenomenon of spasm during bronchography should be more generally appreciated by those responsible for diagnosis and treatment of patients with chronic cough. Though such a picture might

be anticipated in a small percentage of patients with an asthmatic history, it is of importance to recognize the bronchographic pattern of spasm in the nonasthmatic individual. It seems advisable to review the basic points characteristic of both bronchospasm and bronchiectasis in order to alert the unwary to the possibility of confusing the two conditions.

The cases presented clearly demonstrate the fallacy of a single bronchographic study and show how bronchospasm misinterpreted as bronchiectasis might easily lead to unwarranted excisional surgery.

The bronchographic picture attributable to bronchospasm is characterized by the following features: (1) Bronchial dilatation of a hydrostatic nature occurs within the primary and portions of the secondary division bronchi. (2) Spasm of the tertiary and distal bronchi produces a horizontal obstruction to the flow of the contrast medium; consequently the spastic bronchi do not fill. (3) The normal space relations are maintained between the first and second division bronchi, indicating the existence of aerated lung parenchyma. (4) Bronchiolar and alveolar filling is only patchy when evident distal to the zone of dilatation. (5) Proximal narrowing of a major bronchus is never visualized.

The following characteristics are essential to the bronchographic recognition of bronchiectasis: (1) cylindrical dilatation of a marked degree with complete loss of normal tapering tendency; (2) saccular areas in direct continuity with the dilated bronchus; (3) crowding of the bronchi resulting from decreased space occupied by pulmonary parenchyma of the involved area; (4) a decrease or complete absence of bronchiolar and alveolar filling; (5) proximal bronchial narrowing which may or may not be evident.

The horizontal obstruction to flow evident in the initial bronchogram is not encountered in the markedly dilated bronchus of bronchiectasis. The maintenance of normal space relations between the several bronchi as determined by their position and direction in bronchospasm is not evident in bronchiectasis where in the functionless parenchyma permits a crowding and downward depression of the bronchi. These particular points are basic in differentiation of bronchospasm and bronchiectasis.

It would appear, therefore, that repeat bronchography with special medication is essential in differentiating bronchial distension due to spasm from bronchiectasis; and that conference consideration of bronchograms is of value in preventing unnecessary surgery due to misinterpretation of a single bronchographic study. S. J. SHANE

Tuberculosis in Hospital Employees as Affected by an Admission Chest X-Ray Screening Program.

G. JACOBSON *et al.*: *Dis. Chest*, 32: 27, 1957.

Tuberculosis represents a distinct occupational hazard to general hospital employees. This danger has been attested by the fact that from 1942 through 1955, 90 employees of the Los Angeles County Hospital were awarded compensation for tuberculosis. Five of these patients are known to have died of their disease. The incidence was six times as high among those having close contact with patients (i.e., physicians, nurses, attendants, laboratory technicians, etc.) as among clerical and other non-exposed personnel.

Since the institution of a routine admission chest x-ray screening program in the latter part of 1951, the danger of an employee's contracting tuberculosis has almost disappeared. The incidence of newly developed disease among employees has dropped to less than one-fifth of the former rate and not one instance has been found so far among those who began to work at the hospital after 1952. The early recognition and isolation of patients with hitherto unsuspected tuberculosis on the general wards of the hospital should be emphasized as the most important means of reducing personnel exposure and infection.

The saving in compensation alone has already amounted to more than the cost of the entire admission chest screening program. S. J. SHANE

The Cause of Death in Patients with Laennec's Cirrhosis.

J. B. WALLACH *et al.*: *Am. J. M. Sc.*, 234: 56, 1957.

In 8676 consecutive necropsies performed in a large general hospital from 1936 to 1950 inclusive, 300 cases of portal cirrhosis (3.5%) were found. One hundred and thirty-one (43%) deaths were directly attributable to the liver disease. These included 63 patients who died from bleeding œsophageal varices, 13 from primary carcinoma of the liver, and 5 from thrombosis of the portal vein or its branches; in 50 cases death was due to liver failure. Cirrhosis was a significant contributory disease in many additional cases.

These cases were tabulated and compared with more than 2300 previously reported cases of cirrhosis. Considerable variation in the clinical series stressed the frequency of deaths due to liver failure and bleeding œsophageal varices; the significance of infection as a cause of death was underemphasized. This was due to clinical inadequacies as well as the different criteria used for the selection of cases.

Liver failure and bleeding œsophageal varices each accounted for 15 to 20% of all deaths in patients with portal cirrhosis; infection and miscellaneous causes (particularly cardiovascular and cerebral) were each responsible for 25 to 30% of the fatalities. S. J. SHANE

Cardiac Complications of Infectious Mononucleosis.

B. H. WEBSTER *et al.*: *Am. J. M. Sc.*, 234: 62, 1957.

The literature concerning cardiac complications of infectious mononucleosis is reviewed, and five cases of cardiac involvement in infectious mononucleosis proven by hæmatological and serological criteria are discussed.

The cases include four white males and one female. These include a 17-year-old boy with acute pericarditis and myocarditis; a 57-year-old man with

acute pericarditis; a 30-year-old female with acute myocarditis, hepatitis, and pneumonitis; and a 17-year-old boy with acute pericarditis. All cases were self-limited, clearing spontaneously in six weeks to four months. Treatment was symptomatic and supportive, with bed rest. S. J. SHANE

SURGERY

Diagnostic Surgical Procedures for Pulmonary Disease.
H. P. LONGSTRETCH *et al.*: *Dis. Chest*, 31: 575, 1957.

It is imperative to establish the diagnosis in undetermined pulmonary lesions and to resort to one of several surgical biopsy procedures, provided the clinical aids of fungal and tuberculin skin tests, smears and cultures of sputum, gastric washings, aspirated bronchial secretions and of material from pleural and pericardial cavities, as well as fungal serological studies, have been of little or no value.

The authors concluded that diagnostic thoracotomy was of the greatest value. It should not be delayed unnecessarily, since it can be done with considerable safety.

In this series, fat pad, pleural and pericardial biopsies did not aid in the determination of the etiology of the underlying disease in the majority of the cases. These results differ greatly from those reported in the medical literature. It is clear, therefore, that one can save the patient with undiagnosed pulmonary disease considerable inconvenience and possibly improve the prognosis by earlier surgical intervention. The practice of "watchful waiting", still quite prevalent, is no longer justifiable.
S. J. SHANE

Meconium Ileus and Meconium Peritonitis.
P. F. FOX AND W. J. POTTS: *A.M.A. Arch. Surg.*, 74: 733, 1957.

Meconium ileus is an intestinal obstruction in the newborn and is a manifestation of fibrocystic disease of the pancreas. Meconium peritonitis is usually due to a prenatal perforation of the distended intestine proximal to a meconium obstruction, but it can occur without obstruction. Characteristically there is vomiting, abdominal distension, and failure to expel meconium stools. Abdominal wall veins are usually distended and the distal rectum is narrowed. Masses may be palpable in the right lower quadrant. Radiographs of the abdomen show dilated loops of small bowel without fluid levels unless there are complications. In meconium peritonitis there is often calcium in the peritoneal cavity.

Treatment by enterotomy, removal of thick meconium and instillation of a solution of pancreatic substance may have to be added to for volvulus, gangrene or perforation.

At the Children's Memorial Hospital in Chicago there were 13 cases in six years. Three out of five patients with peritonitis died. The prognosis after a successful operation depends on successful management of the fibrocystic disease, especially of the pulmonary involvement. Successful treatment of meconium ileus and peritonitis is a recent achievement. BURNS PLEWES

Antral Exclusion with Vagotomy for Duodenal Ulcer.
W. R. WADDELL AND M. K. BARTLETT: *Ann. Surg.*, 146: 3, 1957.

The side effects of the present operative procedures for duodenal ulcer such as blowing of the duodenal stump, pancreatitis, common duct injury, later gastrectomy syndromes, loss of weight and strength and recurrent ulceration, have led to a search for a more universally adequate operation. This is a report on 100 patients who were operated upon to remove the gastric antrum and divide the vagus nerves.

The technique of the operation is described in detail. The vagi are resected under direct vision. Half the stomach is removed, leaving the pylorus, and an anterior gastrojejunostomy is done after closing the lesser-curve half of the gastric stump.

Secretory studies showed a depressed acidity in spite of stimulation by broth, histamine and insulin. But a few of these patients have dumping syndrome, weight loss, or other troubles. Further time must be allowed to elapse before final evaluation of this operation. BURNS PLEWES

Carcinoma of the Breast: Results of Surgical Treatment.
E. M. ALRICH, H. V. LIDDLE AND C. B. MORTON: *Ann. Surg.*, 145: 799, 1957.

A 5-year and 10-year follow-up of cases of carcinoma of the breast treated at the University of Virginia Hospital between 1929 and 1951 included 448 cases. The over-all five-year survival rate was 50%. Location of the primary in various parts of the breast seemed to have no influence on survival, so that it seems that extension of the classical radical mastectomy to internal mammary or supraclavicular areas would not increase the survival rate.

The 5-year survival rate without clinical recurrence after radical mastectomy was 54%, the 10-year rate 42%.

With the exception of adenocarcinoma, the pathological type and grade of the tumour had little influence on the outcome, but the presence of axillary metastases was an important factor. In some cases of premenopausal breast cancer, castration seemed to lengthen survival, but there is no way of predicting which persons would be thus benefited.
BURNS PLEWES

THERAPEUTICS

Atrial Fibrillation of Many Years' Duration Regularized by Quinidine.
E. RISS AND S. A. LEVINE: *Am. J. M. Sc.*, 233: 654, 1957.

The case histories of two brothers with long-standing atrial fibrillation and no other evidence of heart disease are recorded. In one, the arrhythmia was known to have lasted for 17 years; in the other, for at least five years. In addition, the son of one of the brothers has the same condition.

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In both cases huge doses of quinidine were necessary and effective in restoring the heart to normal sinus rhythm (the first case receiving increasing amounts up to a single dose of 2.0 g. and the second case up to 1.5 g.). In one reversion has been maintained for five years, in the other for three years.

The merits and desirability of quinidine therapy in this group are discussed. S. J. SHANE

Clinical Evaluation of Peganone, a New Anticonvulsant.

C. H. CARTER *et al.*: *Am. J. M. Sc.*, 234: 74, 1957.

After a control period of one year on established therapy, 38 chronic, refractory, institutionalized epileptics were treated with 3-ethyl-5-phenylhydantoin (Peganone). There was an over-all improvement of 62% in the number of seizures. Seventy-one per cent of the cases showed a reduction of more than 50% in the number of seizures.

Routine blood studies, liver function tests and urinalyses were carried out on all patients. There were no deviations from normal, and no evidence of other toxic effects such as gum hyperplasia or skin rash. The only side effect noted was some drowsiness on very high dosages (in excess of 4.5 grams daily). A significant improvement in control was achieved in this group by the addition of Peganone to the existing regimen, or (in many cases) by its use alone. Peganone is a most valuable addition to those drugs currently available, because of its effectiveness and lack of toxicity. S. J. SHANE

Chlorpromazine-Induced Jaundice with Continued Use of the Drug.

S. J. SKROMAK *et al.*: *Am. J. M. Sc.*, 234: 85, 1957.

In 2 cases of chlorpromazine-induced jaundice the drug was continued inadvertently without evidence of untoward effects. The clinical picture of jaundice cleared and it did not recur despite continued therapy. This observation therefore raises the question as to the necessity of discontinuing therapy because of the appearance of jaundice. The ability to continue chlorpromazine therapy, despite the appearance of jaundice, would be of some selective therapeutic value, especially in neuropsychiatric patients. This procedure may be followed only if the patient is hospitalized, and close clinical observation and laboratory facilities are available. The purpose of continuing therapy under such circumstances would be to supplement the present study and confirm these observations, the validity of which would enhance the scope and usefulness of a therapeutic agent.

The writers speculate on the possibility of a temporary interference, or relative insufficiency of cortisone activity in the liver cell or bile canaliculi in patients who develop jaundice on chlorpromazine therapy, and the possibility of reversing chlorpromazine-induced jaundice by cortisone therapy.

It is suggested that with strict control in hospital, such jaundiced patients might be cautiously continued on this therapy, since additional evidence is necessary to confirm these observations before recommending this practice. S. J. SHANE

INDUSTRIAL MEDICINE

Guiding Principles of Medical Examinations in Industry.

THE COUNCIL ON INDUSTRIAL HEALTH: *J. A. M. A.*, 161: 975, 1956.

When properly conducted, medical examination programs provide many benefits to employees, employers, and the community. Placement of individuals according to their abilities, together with assistance in the maintenance of their health, is stressed in this report—the guiding principles of industrial medical examinations as approved for publication by the Council on Industrial Health.

It is essential to the success of the medical examination program that the physician-patient relationship be maintained with fairness to both employee and employer. The role of the physician is important. His duties include acquisition of first-hand knowledge regarding the various jobs within his industry, conduct of the examination, interpretation of medical findings with regard to work significance, and health counselling.

Flexibility according to need is emphasized in the best type of examination program, the scope of the examination varying with the nature of the industry, its inherent hazards, the variation in jobs, and the physical demands and health exposures. The present trend is towards more thorough examinations. The various kinds, classified as original, periodic and special, are discussed with reference to purpose, nature and frequency. Attention is drawn to the examinations of executives—a special type of periodic examination now becoming more prevalent.

There are many examination report forms now in use. The desired detail and arrangement is a matter for decision by the doctor after consultation with management relative to the scope of the examination. The information derived may properly be put by him to several uses involving at times the worker, the employer, another physician or health agency, and/or governmental agencies such as courts or workmen's compensation commissions. In all other aspects the confidential character of health examination records should be rigidly observed and access granted only on written consent of the worker, preferably after discussion with the examining physician.

It is the prerogative and duty of management to inform the applicant whether he is to be employed. The physician should give the employer certain placement information. The plan or rating method agreed upon will enable the physician to convert medical findings into meaningful industrial terminology. Many systems of rating are now in use.

From the public and industrial health standpoint the only bars to immediate employment in non-hazardous occupations should be communicable disease, incapacitating injury or diseases, and mental illness in which impaired judgment or actions prevent co-operative effort. MARGARET H. WILTON

OBITUARIES

DR. LEONARD SHELDON BARTLETT, a physician at Hamilton, Ont., died in August. He was born in Ravenswood, Ont., and graduated from McGill University, Montreal, in 1934. Dr. Bartlett, who was a member of the staff of St. Joseph's Hospital, Hamilton, was in general practice at Mount Elgin before going to Hamilton in 1952.

He is survived by his widow, a son and a daughter.

DR. CLAUDE BISSON, 38, a practitioner at Bonnyville, Alta., died in Edmonton on August 7. He was born in St. Edward, Alta. During the war he served with the R.C.A.F. and returned to study medicine at the University of Alberta, where he graduated in 1952.

Dr. Bisson is survived by his widow and five children.

DR. JOHN McKAY COLE died in Windsor on September 1. He was born in London, Ont., where he received his primary and secondary education. He graduated in medicine from the University of Western Ontario in 1928, interning in the Children's and Grace Hospitals, Detroit. The following two years were spent in postgraduate work in radiology in the University of Michigan Hospital. During the next six months he visited in various radiological centres in Europe. He commenced the practice of his specialty in Windsor in 1932 and soon afterwards was placed in charge of radiology in Hôtel-Dieu Hospital, a position he held until his untimely death. He was a member of the Essex County Medical Society, the Ontario and Canadian Medical Associations, the Detroit Radiological Society, and the Canadian Association of Radiologists.

Dr. Cole is survived by his widow, a son and a daughter.

DR. HUGH M. MacDONALD, who had been a coroner at Oshawa, Ont., for more than 20 years, died at Sunnybrook Hospital, Toronto, on September 4. He graduated from Queen's University, Kingston, Ont., in 1914. During World War I he served overseas with the R.C.A.M.C. In Oshawa he was on the staff of the General Hospital, and had acted as coroner and medical adviser for the Oshawa police department and for Canadian National Railways.

Dr. MacDonald is survived by two sons.

DR. CHARLES ALEXANDER MORRISON, 81, died at Kingston, Ont., on August 12 after a long illness.

Born in Kingston in 1876, Dr. Morrison attended the Academy there and then went on to Queen's University, where he was an honours graduate in medicine in 1898. After serving as an intern at the Polyclinic Hospital, New York City, he returned to Kingston to become Assistant Professor of Surgery at Queen's University. During World War I, he served with the Royal Canadian Army Medical Corps. He also was surgeon for the Canadian National Railways in Kingston. He retired 20 years ago.

He is survived by two sons and two daughters.

DR. LUCIEN ERIC ROBIDOUX, 80, died at the Hotel Dieu Hospital, Moncton, N.B., on August 11, after a long illness.

Dr. Robidoux was born at Grand Digue on May 17, 1877. He attended St. Joseph's University and from there went on to McGill University, from which he graduated in medicine in 1901. He first went into practice at Rogersville in Northumberland County, but moved shortly afterwards to Shediac to practise there, and in adjacent districts in Westmorland and in southern Kent county, until forced by ill health to discontinue practice some months ago.

He is survived by four sons and three daughters.

DR. WILLIAM A. CRAIG WATSON, a practitioner in Toronto, died suddenly on August 28. He was born at Verona, Ont., and graduated from Queen's University, Kingston, Ont., in 1929. He practised at Granby, Que., before moving to Toronto. During World War II he served as a medical officer with the R.C.A.F.

Dr. Watson is survived by his widow.

Dr. William Easson Brown: an Appreciation

H.J.S. writes:

DR. WILLIAM EASSON BROWN died suddenly at his summer home in Muskoka, on August 30, the last day of his summer vacation. Unknown to most of his friends he had had some warnings of possible future troubles but his was the breed that would carry on life's usual functions without change and without regrets. In his last holiday he worked about his cottage even to the extent of activities involving some degree of manual labour. His was a busy life, too full possibly for his own good, with many interests apart from medical activities which he followed with intense zeal.

As a boy at High School (Harbord) and in his University period he was active in sports, particularly in track in which he was a keen competitor. He had an impressive record in the sprints in which he won many points for his teams. His interest in athletics in general and the University Track Club in particular was maintained to the end. He never missed a meeting of the Track Club and for years he officiated at the inter-university track meets. He was a member of the Athletic Directorate of the University of Toronto for many years, a position he still held at the time of his death and one to which he devoted considerable time and thought.

Civilian flying was another of Dr. Brown's activities. Through the Toronto Flying Club he obtained his flying licence in 1929 and until recently

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he piloted aeroplanes and seaplanes. He gave many of his friends a thrill and on occasion he flew a seaplane to his summer home. His association with the Flying Club gave rise to his appointment as medical examiner of flying personnel. He belonged also to the Aero Medical Society and the Civil Aviation Association.

Dr. Brown will be remembered longest for his research activities with reference to anæsthetic substances. While associated with the Department of Pharmacology and Professor Velyen Henderson he initiated studies with ethylene, and with Professor George Lucas introduced the gas cyclopropane which is still widely used in the civilized world. As a clinical anæsthetist he was fearless in applying new techniques whether his own invention or in investigation of methods reported in other centres. These sorties into new fields were always preceded by careful study or animal experimentation. He contributed a number of articles to various journals of anæsthesia.

"Bill", as he was known generally to his friends, was born the son of a doctor in Western Ontario. For a time the family lived in Chicago, eventually returning to Toronto where the boy grew up. From Harbord Collegiate in that city he entered medicine at the University of Toronto, graduating M.B. in 1916. He served overseas as Captain in the C.A.M.C. at the Canadian Hospital at Orpington in England, in which hospital he began his anæsthetic career. On his return from his overseas duties he was appointed to the Anæsthesia Department of the Toronto General Hospital, a post he retained until he reached the retiring age, at which time he was named consultant in anæsthesia to the hospital.

He was the recipient of many honours during his lifetime. He was granted the M.A. degree by his university for his thesis on ethylene, and the Diploma of Anæsthesia by the conjoint board of the Royal College of Physicians and Surgeons (England) in 1938. He was a member of the Toronto Academy of Medicine, the Canadian Anæsthetists' Society, and the American Society of Anesthesiologists. He was a charter member of the Anæsthetic Travel Club, now the Academy of Anæsthesiologists. He belonged to the Aero Medical Society and was an Honorary Member of the Toronto Medico-Legal Society. He was also an original member of the Caduceus Club, a Toronto medical dinner society. From these activities he found time to act as Assistant Coroner for the City of Toronto. He was a cheerful soul with ever a joke or anecdote suitable for the occasion. His presence was felt in any company in which he found himself.

Our deepest sympathy goes to his widow, the former Irene Gallagher; and his three children, James Easson of Norval, Ontario, Frederick Wallace at present in Casablanca, Morocco, and Patricia of Toronto. A third son, William, lost his life in the Second World War while serving as a gunner in the R.C.A.F.

FORTHCOMING MEETINGS

CANADA

CANADIAN SOCIETY FOR THE STUDY OF FERTILITY, Annual Meeting, London, Ontario. (Dr. Morris P. Wearing, Secretary Treasurer, 289 Dufferin Ave., London, Ont.) November 8-9, 1957.

CANADIAN MEDICAL ASSOCIATION, 91st Annual Meeting, Halifax, Nova Scotia. (Dr. A. D. Kelly, General Secretary, The Canadian Medical Association, 150 St. George Street, Toronto 5, Ont.) June 15-19, 1958.

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS, 2nd Congress, Montreal, P.Q. (Professor Léon Gérin-Lajoie, Suite 313, 1414 Drummond Street, Montreal, P.Q.) June 22-28, 1958.

UNITED STATES

FOURTH PAN AMERICAN PHARMACEUTICAL AND BIOCHEMICAL CONGRESS, Washington, D.C. (Dr. George B. Griffinhagen, Executive Secretary of the Congress, Smithsonian Institution, Washington 24, D.C.) November 3-9, 1957.

CONGRESS OF NEUROLOGICAL SURGEONS, Washington, D.C. (Dr. Philip D. Gordy, Secretary, 1007 Delaware Ave., Wilmington, Del.) November 7-9, 1957.

PAN AMERICAN ASSOCIATION OF OPHTHALMOLOGY, 5th Interim Congress, New York, N.Y. (Dr. William L. Benedict, 100 First Avenue Building, Rochester, Minnesota.) February 1, 1958.

INTERNATIONAL COLLEGE OF SURGEONS, 11th Biennial Congress, Los Angeles, California. (Dr. Karl A. Meyer, Secretary, 1516 Lake Shore Drive, Chicago 10, Illinois.) March 9-14, 1958.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY, 32nd Congress, New Orleans, Louisiana. (Dr. A. William Friend, Executive Secretary, 227 Wade Park Manor, Cleveland 6, Ohio.) March 24-27, 1958.

INTERNATIONAL SOCIETY OF GASTROENTEROLOGY, 3rd World Congress, Washington, D.C. (Dr. H. M. Pollard, University Hospital, Ann Arbor, Michigan.) May 25-29, 1958.

AMERICAN MEDICAL ASSOCIATION, Annual Meeting, San Francisco, California. (Dr. George Lull, 535 North Dearborn Street, Chicago 10, Ill.) June 23-27, 1958.

OTHER COUNTRIES

CONGRESS OF THE INTERNATIONAL SOCIETY OF SURGERY, Mexico City, Mexico. (Dr. L. Dejardin, 141, rue Belliard, Brussels, Belgium.) October 27-November 2, 1957.

PAN AMERICAN CONGRESS OF ENDOCRINOLOGY, Buenos Aires, Argentina. (Secreteria General, Sociedad Argentina de Endocrinologia y Metabolisma, Santa Fe 1171, Buenos Aires, Argentina.) November 3-9, 1957.

BAHAMAS MEDICAL CONFERENCE, Nassau, Bahamas. (Dr. B. L. Frank, 1290 Pine Ave. West, Montreal, P.Q.) December 1-15, 1957.

INTERNATIONAL ACADEMY OF LEGAL MEDICINE AND SOCIAL MEDICINE, 5th International Congress, Madrid, Spain. (Professor B. Piga, Secretary General of Congress, Professor of Legal Medicine, Madrid University, Madrid, Spain.) April 16-19, 1958.

INTERNATIONAL SOCIETY OF UROLOGY, 11th Congress, Stockholm, Sweden. (Dr. G. Giertz, Secretary General, Karolinska Sjukhuset, Stockholm 60, Sweden.) June 25-July 1, 1958.

COMMONWEALTH HEALTH AND TUBERCULOSIS CONFERENCE, 5th Congress, London, England. (National Association for the Prevention of Tuberculosis, Tavistock House, Tavistock Square, London, W.C.1, England.) July 1-4, 1958.

PROVINCIAL NEWS

PRINCE EDWARD ISLAND

Two new hospital units have recently been added to the available hospital services in Prince Edward Island. The new community hospital at O'Leary with 40 beds brings hospital services to this community for the first time.

The Hillsborough General Hospital, a new active treatment unit operated by the Provincial Government in conjunction with Riverside Hospital for the mentally ill, was formally opened a few weeks ago.

Dr. H. Neil Boyd, who has been pathologist with the Provincial Laboratories for more than a year, has accepted a post as Director of Laboratories at Holy Cross Hospital in Calgary, Alberta. At the moment the province is without a pathologist.

Dr. John Theriault, who is attached to the Provincial Division of Mental Health, has opened an office for the private practice of psychiatry. He continues on a part-time basis with the Provincial Government.

Dr. N. R. Bruvels, who comes from Latvia, has opened an office at O'Leary for the practice of surgery.

Dr. Malcolm Putnam, who has been practising in Brockville, will soon join the surgical staff of the Polyclinic in Charlottetown.

Another member of the Island's best known medical family has joined the ranks of the Island's doctors. Dr. Kenneth Grant is practising with his father, Dr. Roy Grant, in Summerside.

Over 80% of the Province's doctors turned out to welcome Dr. and Mrs. Morley Young on their recent visit to our Island. We were happy to welcome Dr. and Mrs. Arthur Kelly, who accompanied them. Beautiful weather, large attendance, high-calibre scientific sessions, well-prepared reports and well-conducted business sessions all were enlivened by one of our most successful social and entertainment programs and made the 1957 meeting an outstanding success.

The medical ball held at Government House with the Society as guests of His Honour Governor Prowse was an event long to be remembered.

The President's chicken barbecue at his beautiful summer house was enlivened by the Highland music and dancing of the famous Burke Family Pipe Band.

Summary of Program

On the first day, Friday, August 23, the program began with a business session and continued with a lunch at P.E.I. Hospital, at which the chairman was Dr. T. A. Laidlaw, and the guest speaker, Dr. Morley Young. The afternoon session included papers by Dr. K. J. R. Wightman of Toronto on problems in the use of antibiotics, and Dr. H. L. Richard of Ottawa on the present status of surgical treatment of thyroid disease.

The business session continued on the Saturday, and was followed by a paper on staphylococcal infections in hospitals, by Dr. K. J. R. Wightman. The luncheon was at the Charlottetown Hospital, with Dr. J. A. MacMillan in the chair, and Dr. A. D. Kelly, General Secretary of the C.M.A., as speaker. The afternoon session contained papers by Dr. Richard on the present status of surgical treatment of breast cancer and Dr. Wightman on chemotherapy in malignant disease.

At the business sessions the following officers were elected: *President*—Dr. L. E. Prowse; *1st Vice President*—Dr. J. H. Maloney; *2nd Vice President*—Dr. T. A. Laidlaw; *Honorary Secretary*—Dr. Frank MacMillan; *Honorary Treasurer*—Dr. R. G. Lea; *Executive Secretary*—Dr. F. L. Whitehead. *County Representatives on Executive Committee*—Prince: Dr. L. G. Dewar; Queens: Dr. C. A. Coady; Kings: Dr. E. Kassner. *Chairman of Committee on Economics*—Dr. J. H. Maloney. *Representative on C.M.A. Executive*—Dr. J. A. MacMillan. *Society's delegates to General Council, C.M.A.*—(the President and Secretary automatically) Dr. L. E. Prowse, Dr. Frank MacMillan, Dr. J. A. MacMillan (P.E.I. nominee to C.M.A. Executive), Dr. L. G. Dewar, Dr. R. G. Lea (alternate to C.M.A. Executive), Dr. A. R. Grant, Dr. T. A. Laidlaw (delegate to 1958 C.M.A. Nominating Committee), Dr. W. J. P. MacMillan (alternate to 1958 C.M.A. Nominating Committee). *Members of Medical Council of P.E.I.*—Dr. R. G. Lea, Dr. J. H. O'Hanley, Dr. E. M. Found, Dr. F. MacMillan, Dr. W. Moreside, Dr. R. A. Reid, Dr. O. H. Curtis.

His many friends will be pleased to learn that Dr. Rupert Seaman is now convalescing from his recent illness.

Dr. Tadeusz A. Schimanek, a refugee from Hungary in December 1956, who has been at the Scarborough General Hospital, has been accepted as resident at the Charlottetown Hospital.

J. A. McMillan

CANADIAN ARMED FORCES

Colonel E. J. Young, C.D., Eastern Command, has been seconded to the Department of National Health and Welfare (Civil Defence), and commenced his new duties on September 16.

Colonel G. L. M. Smith, C.B.E., C.D., who has recently attended the National Defence College at Kingston, Ont., has been appointed Commandant, The R.C.A.M.C. School, Camp Borden, Ont.

Group Captain D. G. M. Nelson, C.D., has graduated from National Defence College, Kingston, and has resumed his duties as Commanding Officer, Institute of Aviation Medicine, Toronto.

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Major R. N. Hetherington, now serving in the Middle East, has been promoted to Lieutenant-Colonel and appointed Senior Medical Officer, Canadian Detachment, United Nations Emergency Force Middle East, to replace Lieutenant-Colonel J. S. Hitsman, who has returned to Canada and is stationed at Kingston.

Wing Commander H. B. Hay, D.S.O., D.F.C., C.D., has completed postgraduate training at Harvard University and has been transferred to Air Transport Command Headquarters, Lachine, P.Q., as Staff Officer of Medical Services.

Wing Commander R. H. Lowry, A.F.C., C.D., has completed postgraduate training at Johns Hopkins University and has been transferred to Air Materiel Command Headquarters, Ottawa, as Staff Officer of Medical Services.

BOOK REVIEWS

PERSONALITY, STRESS AND TUBERCULOSIS. Edited by Phineas J. Sparer, Professor of Psychiatry and Preventive Medicine, University of Tennessee College of Medicine. 629 pp. Illust. International Universities Press Inc., New York, 1956. $12.50.

This book should be in the library of every sanatorium for the treatment of tuberculosis and should be read by every professional person engaged in the care of the tuberculous. It is a compendium of current thought on the influence of many factors other than the tubercle bacillus in determining the course of a tuberculous infection. The editor is both a chest physician and a psychiatrist. The authors of the 33 chapters cover an imposing array of subjects, to which a great deal of thought and painstaking investigation has been given by those who are leaders in their fields. The book is divided into four sections: (1) basic considerations; (2) clinical applications; (3) special problems; and (4) a program.

Psychosomatic medicine, endocrinology, neurology, psychology, personality and stress are covered in section 1; case reports abound. In the second section the patient is regarded from every viewpoint, including his own inner world, in order to help him meet his various problems. The demands made on various sections of the medical staff and related personnel during and after his hospital stay are recognized. Under "special problems" much attention is given to the underlying causes of irregular discharges, their predictability and their prevention, including a chapter from the Royal Edward Institute at Montreal. The alcoholic tuberculosis patient is studied from many angles, including his own "skid row" environment, and much light is thrown on his behaviour. Finally, Dr. Sparer outlines a comprehensive service, including psychosomatic medicine, for the treatment of people who have to be in hospital because of their tuberculosis.

This is the briefest possible coverage of a 600-page volume in which every chapter is a complete unit in itself, written by its own author (of which there are 34), and so can be read independently of the adjacent chapters, to obtain information on the special subject to which it is devoted.

LECTURES ON THE SCIENTIFIC BASIS OF MEDICINE: Vol. V, 1955-1956. British Postgraduate Medical Federation, University of London. 473 pp. Illust. The Athlone Press, University of London, 1957. 45s.

The present volume of this series contains 26 of the lectures arranged by the British Postgraduate Medical Federation in 1955-56, to acquaint clinicians with advances in clinical science. The field covered seems to be wider than ever. The obstetrician will find discussions of physiological effects of anoxia in the fetal and newborn lamb, the oxygen environment of the human fetus, and isotopes in the study of problems of pregnancy. The anæsthetist and the cardiac surgeon will find lectures on experimental hypothermia in animals and on the effects of cold on man. The pharmacologist will find lectures on the elucidation of toxicity and on industrial toxicology, as well as a host of material on various aspects of biochemistry. All will be interested in Dr. Loutit's study of recovery from the lethal effects of radiation, and specialists in internal medicine will appreciate the articles on treatment of hepatic coma, investigation of gastric digestive function in man, renal control of acid-base balance, and a number of other contributions. Even the otolaryngologists are not forgotten, for Dr. Slome contributes a study of the physiology of the nasal circulation. The standard of production is as high as usual, and the quality of the writing excellent.

ATLAS OF CLINICAL ENDOCRINOLOGY. H. Lisser and Roberto F. Escamilla, University of California School of Medicine. 476 pp. Illust. The C. V. Mosby Co., St. Louis, Mo., 1957. $18.75.

This book adequately achieves the primary purpose of its authors, to "offer a concise and largely visual presentation of endocrine disorders in Atlas format, with abbreviated text which contains all essentials for adequate diagnosis and therapy, even to details of dosage". The section on the pituitary gland is exceptional, and rich with historical material that adds considerable interest to the text. The illustrations, for the most part photographs of patients and radiographs, reflect the vast clinical experience of the authors.

The text is very brief but on the whole very complete, although in places it suffers a little from the oversimplification that such brevity necessitates. The treatment of hyperthyroidism with radioactive iodine

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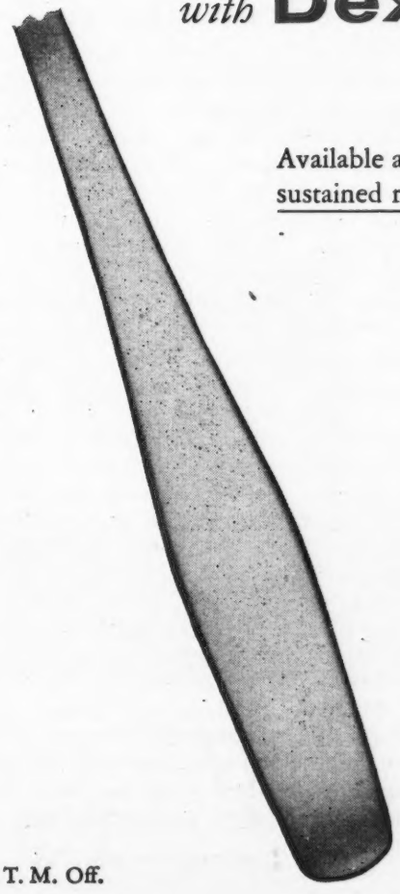

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does not receive quite the enthusiastic appraisal that it has found in most texts. Many conditions which are not truly endocrine, but which are often a problem in the differential diagnosis of endocrine disturbances, such as progeria, gargoylism, and mongolism, are covered in some detail. The appendix contains many useful tables and charts invaluable in assessing the development of a patient. Heights and weights, growth curves, mentality charts, and bone-age tables are given. The bibliography is sufficient to introduce the reader to the classical literature on the subject and to give him the most recent findings in this field.

This book should certainly serve as an excellent introduction to endocrinology for students and general practitioners. Because it depends for the most part on pictorial material, its value should continue longer than that of other texts on the subject. The clinical appearance of the endocrine diseases will not change, though our understanding of them may. This text will be a welcome addition to any library and should be readily available to any practising internist.

SURGERY: Principles and Practice. Edited by J. Garrott Allen, University of Chicago; Henry N. Harkins and Carl A. Moyer, Washington University School of Medicine, St. Louis, Mo.; and Jonathan E. Rhoads, University of Pennsylvania School of Medicine and Graduate School of Medicine, Philadelphia. 1495 pp. Illust. J. B. Lippincott Company, Philadelphia and Montreal, 1957. $16.00.

The four editors of this new and important textbook of surgery disarm criticism of the appearance of a new student text in their first sentences by suggesting that there is need for a surgical textbook including more discussion than usual of the physiological, biochemical, pathological and anatomical bases of surgery. Six objectives are listed: (1) the provision of an introduction to general surgery and the specialties, except ophthalmology and otorhinolaryngology; (2) propagation of the idea that surgical practice is neither standardized nor perfected; (3) emphasis on important aspects of contemporary surgery (there are excellent sections on military and cardiovascular surgery); (4) emphasis on surgery in general rather than techniques (though the commonly performed operations, such as radical mastectomy, are described in detail); (5) thorough discussion of surgical physiology as a basis of nonoperative care; (6) evaluation of results of present-day surgery.

It would seem that these objectives have been reached. A sound textbook has been achieved with stress on the important and common conditions; for instance, there are as many pages on hernia as on the whole of neurosurgery, while fracture treatment occupies a vast space in comparison with nontraumatic orthopædics. The chapter on radiation injury is a grim reminder of our latest menace; on the other hand, our old acquaintance, appendicitis, requires just as many pages as ever, and the gridiron incision still gets a full description after over 60 years of popularity.

In summary, this new book, with contributors from every section of the United States, has all the earmarks of a successful student text.

LEHRBUCH DER CHIRURGIE (Textbook of Surgery). Edited by H. Hellner, Göttingen, R. Nissen, Basel, and K. Vossschulte, Giessen. 1059 pp. Illust. Georg Thieme Company, Stuttgart; Intercontinental Medical Book Corporation, New York, 1957. $20.00.

A co-operative effort by surgeons from 19 centres in Switzerland and West Germany produced this textbook for students and general practitioners within a year. The result is a fairly traditional text with stress on physiological-pathological principles, clinical features and indications for treatment. Operations are described in very general terms—in fact, the technique of appendectomy is not described at all—and there is a tendency to surgical dogmatism. For example, only one method of treatment for shoulder dislocation is given, without critical discussion of alternatives. Neurosurgery gets an unusually detailed description and thoracic surgery is well covered. The chapter on cardiac surgery is also highly readable, and indicates the importance of the Anglo-Saxon contribution. Gynæcology, ophthalmology and otolaryngology are not represented. History of surgery receives adequate attention and there is a fairly good bibliography.

PATHOLOGY. Edited by W. A. D. Anderson, University of Miami School of Medicine and Jackson Memorial Hospital, Miami, Florida. 1402 pp. Illust. 3rd ed. The C. V. Mosby Company, St. Louis, Mo., 1957. $16.00.

The third edition of this well-known text on morbid anatomy is presented in the same format as the previous edition; it has roughly the same number of pages and contains 53 more illustrations and one more colour plate. Three contributors to the 1953 edition who have died have been replaced by five newcomers. The size of the type varies according to the importance of the material. The book can therefore be used both as a text for learning and as a reference.

Two chapters have been completely rewritten. One deals with the hypophysis and comes from the pen of Professor Russell of London; the other, on the female genitalia, was written by two members of the department of pathological anatomy of Harvard Medical School. The section on the adrenal gland, which has been revised and brought up to date, includes a number of references to aldosterone. Several minor changes have been made here and there in the text—a few paragraphs on the effects of small doses of radiation have been added, and one on pneumatosis intestinalis, as well as new illustrations of fusospirochætosis, mucormycosis, and the male genitalia and lower urinary tract. Some eponyms have been dropped, such as Waterhouse-Friderichsen syndrome and Addison's disease; the spelling of a few words has been modernized—eosinophil instead of eosinophile; and minor typo-

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graphical changes made in the printing of the book. One wonders why the bargram shown in Fig. 330 and taken from a 1926 journal, or the U.S.A. map showing the relative death rates of rheumatic fever and dated 1941, have not been replaced by more recent references.

This text is nevertheless one of the best general reference books in pathology, particularly with the extensive reference list at the end of each section brought up to date. Those who already own a copy of the second edition may not consider the changes brought to the third one extensive enough to warrant the purchase of a copy. However, it is recommended to those who have only the first edition or who do not possess the book at all.

ULCERS OF THE LEGS. P. Piulachs, Chief Professor Surgeon in the Faculty of Medicine of Barcelona. 574 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1956. $17.00.

This well-bound and well-illustrated book provides a comprehensive consideration of its subject. Venous, arterial and neurotrophic ulcers are considered. The author presents his views, which indicate his original thinking, convincingly, and brings forth a considerable body of experimental evidence to prove their validity.

It is his view that all superficial venous varicosities, essential as well as postphlebitic, have the same pathogenic mechanism in the beginning, and that both result from an increased blood flow through congenital arteriovenous aneurysms. By means of arteriography this quick passage of the blood from the arteries to the veins can readily be demonstrated. It is postulated that leg ulcers of venous etiology are due to repeated hypertensive pressure waves passing down the venous channels unimpeded by the incompetent valves. These pressure waves then expend themselves in the peripheral tissues with a hydraulic ram effect which gives rise to changes there likely to eventuate in a venous ulcer. These pressure waves are the result of exertions carried out by the individuals while in the upright position.

In the treatment of venous ulcers, in over 90% of which the deep system is involved, a method of "spaced ligations made under manometric control" is recommended. The superficial femoral vein is first divided and then a manometric test is made on the distal segment; if the pressure still rises sharply here on abdominal pressure, the popliteal vein is also transected. If the pressure is still transmitted to the distal segment here, a further large branch is looked for and ligated until the pressure wave is not transmitted to the distal venous section in the popliteal region. To prevent œdema developing following these ligations, the patient is started on heparin four hours postoperatively and kept on it for four days. The superficial saphenous system is later ligated and stripped. Excellent results are claimed for this method, combined with skin grafting of the ulcer if necessary. Sympathectomy in the treatment of venous ulcers is condemned. The problem of club foot due to venous ulcers is considered. A variety of arterial leg ulcers are dealt with, including those associated with Raynaud's disease. Neurotrophic ulcers are also fully discussed.

On the whole this is a very stimulating and valuable reference book which deserves study by any doctor interested in the vexatious problem of leg ulcers.

DIE ERKRANKUNGEN DER GALLENWEGE (Disorders of the Biliary Tract). W. Schöndube, Frankfurt-on-Main. 311 pp. Illust. Ferdinand Enke Company, Stuttgart, 1956.

In this monograph, only the disorders of the bile ducts, gall-bladder, and sphincter of Oddi are considered; liver disorders secondary to disturbances in the biliary tract are included. Recent advances in the radiological study of the bile ducts, in particular Mallet-Guy's radiomanometry of the biliary system and the introduction of the new German drug Biligrafin (Cholografin) for intravenous cholecystography, have increased our knowledge of the physiology and pathology of this system and are discussed fully in this book.

The author begins with a brief note on the anatomy of the bile ducts and their physiology, with special reference to their motility and to the physiology of the bile. In diagnosis, he emphasizes the extreme importance of an accurately taken history, but describes in detail also such aids as duodenal intubation and radiographic investigations. The rest of the book contains a discussion of the clinical features of disorders of the bile ducts and gall-bladder, and their treatment. The clinical descriptions follow standard lines, but some of the drug therapy will puzzle North American readers, since many of the products referred to are proprietary German compounds. The literature is quoted extensively and the book closes with an adequate bibliography of the subject.

THE NEUROHYPOPHYSIS: Proceedings of the Eighth Symposium of the Colston Research Society, April 9-12, 1956. Edited by H. Heller, Department of Pharmacology, University of Bristol. 275 pp. Illust. Butterworth Scientific Publications, London; Butterworth & Co. (Canada) Ltd., Toronto, 1957. $9.50.

It is difficult to imagine that more than a handful of the readers of this journal would find this beautifully produced but highly specialized book of interest. On the other hand, research workers in a variety of fields ranging from neurology to urology will be delighted that the Colston Research Society has made available the transactions of the first international meeting devoted to the posterior pituitary.

Most of the papers describe original work, and an excellent transcription of the discussions that followed the papers is included. Some 60 members from many countries contributed to the Proceedings, Canada being represented by Professor R. L. Noble of the University of Western Ontario.

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STRAIGHT TO THE HEART. A Personal Account of Thoughts and Feelings While Undergoing Heart Surgery. George Lawton. 347 pp. International Universities Press, New York, 1956. $5.00.

This volume describes the experiences of a non-medical psychoanalyst who suffered from aortic stenosis, reached a severe stage of decompensation, and was restored to health by cardiac surgery.

In a short book-jacket review the Reverend Harry Fosdick praises this book as a frank, intimate and detailed account, which "vividly tells the story" and "is beautifully told". Several psychoanalysts, social workers and others also laud this minute and emotional account of the victim's increasing incapacity, his physical and mental struggles to survive, his search for helpful medical advice, his frantic fears and indecision when surgery was finally proposed. Many of the daily difficulties of a cardiac patient are detailed, such as the unpleasant diet, tricks to improve it, the struggle to pursue a normal life against increasingly overwhelming odds and the looming spectre of complete invalidism. The author's account of his hospital stay and especially of his postoperative physical and mental experiences is extremely intimate and personal. Throughout the book the author eulogizes the surgeon and his staff in a manner that makes the most flamboyant advertising man's extravagances appear paltry. A typical "get-together" reunion of surviving patients, for follow-up examinations and general felicitations between staff and patients, is a good description of a custom fast becoming part of the contemporary American scene. In a final chapter the author's wife gives a searching account of her reactions during her husband's illness and his dramatic recovery.

The best parts of the book are those describing the rapid, almost miraculous, advance of cardiac surgery. The value of a team in such work is stressed, and amply demonstrated: basic scientists, physicians, surgeons, technicians, nurses and all members of the hospital staff are essential for success. The need for more funds and facilities as well as for more education for laity and doctors is emphasized and supported by statistics.

The author does not pretend to a detailed knowledge of cardiology or cardiac surgery and is therefore excused certain inaccuracies. His description of his own surgeon as a foremost pioneer in heart surgery is understandable but does scant justice to the real pioneers of a generation ago such as Carrel, Cutler, Beck, Allen, Graham and others in the U.S.A., to say nothing of many others abroad.

HANDBUCH DER ORTHOPÆDIE (Handbook of Orthopædics). Vol. I. G. Hohmann, München, M. Hackenbroch, Köln, and K. Lindemann, Heidelberg. 1185 pp. Illust. Georg Thieme Company, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1957. $42.40.

Since a review of this volume in the Journal (p. 174, July 15, 1957) it has been announced by the publisher that an index to the complete work will be given at the end of Volume IV.

MEDICAL NEWS *in brief*

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CARDIAC DIAGNOSIS BY ULTRASOUND ECHO

Effert of Düsseldorf and his colleagues (*Deutsche med. Wchnschr.*, 82: 1253, 1957) describe their studies with the ultrasound echo procedure in cardiac diagnosis. The procedure is based on the passage of ultrasound waves into the body and their reflection at the boundary between two media, in this case the anterior surface of the heart. Reflected ultrasound gives rise to an echo which can be registered on appropriate apparatus; if the speed of ultrasound in the medium in front of the heart is known, the exact distance of the anterior surface of the heart from the surface can be measured. This method has already been employed for other diagnostic purposes, such as diagnosis of breast carcinoma. Cardiac movements will produce variations in distance from the heart wall to the source of ultrasound, and an ultrasonic echo curve will record these movements. The ultrasonic echo curve of the left atrium shows many similarities to a left atrial pressure pulse. In mitral stenosis, emptying of the left atrium is delayed and this can be demonstrated by a slowed movement of the left atrial wall away from the chest wall, as recorded in the ultrasonic echo curve. The delay correlates with the degree of stenosis. Pericardial effusion can be diagnosed from changes in distance between the anterior cardiac surface and the chest wall. The particular advantage of the method is its complete freedom from risk, compared for example with cardiac catheterization. The authors consider after studying 70 cases of mitral disease that ultrasonic echo cardiography may eventually make direct cardiac studies unnecessary in some cases of mitral disease.

INFORMATION ON PSYCHOPHARMACOLOGY

A clearinghouse of information on psychopharmacology is being established by the Psychopharmacology Service Center of the U.S. National Institute of Mental Health. An extensive collection of the literature in this field, including pharmacological, clinical, behavioral, and experimental studies of the ataraxic, psychotomimetic, and other centrally acting drugs, will be classified and coded to enable the staff to answer a wide variety of technical and scientific questions. As soon as enough materials have been assembled the Center plans to offer bibliographic and reference service as well as the preparation of critical and analytic reviews of special topics in the field.

In order to accelerate the growth of the literature collection the Center invites persons working in this field to provide three copies of any papers that deal with their work — whether reprints, prepublication manuscripts, progress reports, informal mimeographed reports, papers read at meetings, or abstracts. Letters outlining work in progress would also be welcome. Any restrictions that authors may wish to place on the Center's use of their papers will be strictly observed. All materials should be addressed to the Technical In-

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MEDICAL NEWS *in brief*

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formation Unit, Psychopharmacology Service Center, National Institute of Mental Health, 8719 Colesville Road, Silver Spring, Maryland.

MYCOBACTERIA AND MULTIPLE SCLEROSIS

In 1955 some Swiss workers reported their belief that multiple sclerosis was due to mycobacteria, and demonstrated illustrations of acid-fast bacilli obtained from the cerebrospinal fluid of patients with multiple sclerosis. Fust and his colleagues from Basel (*Schweiz. med. Wchnschr.*, 87: 611, 1957) therefore carried out a blind test on specimens of cerebrospinal fluid from patients with multiple sclerosis and patients with other diseases. Out of 74 specimens of CSF of unknown origin, they found 14 positive results and were able to demonstrate mycobacteria microscopically in seven and culturally in seven. The seven strains isolated by culture showed all the properties of tubercle bacilli of human type. Unfortunately, at the end of the test, comparison of results showed that mycobacteria were present in 19.4% of patients with a confirmed disseminated sclerosis, and in 24% of those with other diseases. There is therefore no indication that multiple sclerosis is a special form of tuberculosis.

A further study of the treatment of 25 patients with multiple sclerosis with isoniazid gave negative results.

NEUROLOGICAL RESEARCH FOUNDATION

Information has been received about a new American research foundation, whose objective is to derive financial support for research into the prevention and cure of certain chronic progressive disorders of the nervous system by establishing research fellowships, and by supporting research for work in neurology. This foundation, the National Neurological Research Foundation, Inc., has its headquarters at 3255 N Street, N.W., Washington 7, D.C. It has a distinguished scientific advisory committee. Its aim is to offer fellowships for periods of five years

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MEDICAL NEWS *in brief*

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so that fellows may work in economic security. Administrative expenses are to be kept to a minimum, and the Foundation asks not only for financial support, but for ideas on the formation of committees and chapters throughout the U.S.A. and ideas on how to contact research scientists and students interested in neurological research. Particular diseases in which the Foundation is interested are Parkinson's syndrome, cerebral palsy, multiple sclerosis, amyotrophic lateral sclerosis and muscular dystrophy.

INTERNATIONAL COLLEGE OF SURGEONS

The newly formed European Federation of the International College of Surgeons announces two forthcoming meetings. The first will be in Vienna, October 18-20, 1957, and the second during the World's Fair in Brussels, May 15-18, 1958. About 75 papers will be presented at the Vienna meeting, which is under the direction of Professor Felix Mandl and Professor Leopold Schönbauer of the University of Vienna, and will bring together German, Austrian, Dutch, Swiss and other sections of the I.C.S. Enquiries about this congress may be addressed to Dr. Felix Mandl, Reichsratsstrasse 11, Vienna 1, Austria.

The Brussels congress will bring together twelve national sections of the I.C.S. and the meeting will be held under the auspices of the Belgian section. Arrangements are in the hands of Professor J. H. Oltramare of the University of Geneva and Dr. Leopold Lambert and his colleagues of the Belgian section. Details from the Secretariat, International College of Surgeons, 1516 Lakeshore Drive, Chicago 10, Illinois.

TRANQUILLIZERS IN VETERINARY MEDICINE

The pace of modern living affects not only human beings; domestic animals too are subject to its stress and strains and show the results in their own ways. It is a well-known fact that disturbed hens or

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cows do not produce as many eggs or as much milk as their contented counterparts. Thoroughbred horses are also given to fits of anxiety which closely resemble psychoneurosis. A new drug Covatin or M68 (benactyzine) has recently been used on racing horses with considerable success in improving the disposition of these animals. The same drug has also been used with profit for suppressing nervous lactation in dogs. It is claimed that mean and aggressive dogs can be made friendly if kept on "Paxytal" (formula not given). These facts would possess only an incidental degree of interest if it were not for the fact that it has been proved that substantial amounts of tranquillizers produced for veterinary medicine have been rerouted by illegal means and sold for human consumption. Drug control officers of various governments have been alerted to this and measures are being taken to forestall this traffic. —*Presse méd.*, 65: 1263, 1957.

BONE SODIUM, POTASSIUM AND CALCIUM DETERMINATION

A new method of determining the content of sodium, potassium and calcium in bone has been devised by Norman of McGill University Clinic at the Royal Victoria Hospital in Montreal. It consists in dissolving the specimens in warm nitric acid, after spongy bone, periosteum and marrow have been removed, and running the solution through a column of resin made up of Dowex 50, –400 mesh size, 12% cross-linked, which has previously been treated with 3N hydrochloric acid to free it from extraneous cations. N hydrochloric acid is used as the eluting agent and the sodium and potassium content of the eluate is determined in a Baird flame photometer. (An elution curve must be plotted for each new batch of resin.)

This method can conveniently replace others based on wet or dry washing and repeated calcium precipitations in the form of carbonate or oxalate, primary determination of the calcium content followed by flame photometry of an aliquot with a comparable amount of calcium introduced as a blank, or immediate flame photometry of the mixture derived from a solution of the bone sample disregarding the calcium content. The recovery yield of the method described above is over 93%.—*J. Lab. & Clin. Med.*, 50: 308, 1957.

AWARDS IN RADIOLOGICAL RESEARCH

On behalf of the James Picker Foundation, the U.S. National Academy of Sciences–National Research Council announces the continued availability of funds in support of radiological research. Applications are reviewed by the Committee on Radiology of the Academy–Research Council's Division of Medical Sciences. Final determination of awards is made by the Foundation upon recommendation of the Division.

In line with the interests of the Foundation, the program is oriented towards, but not necessarily limited to, the diagnostic aspects of radiology. Worthy applications in the field of veterinary radiology will be accepted and considered on their merits. Support

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is not restricted to citizens of the United States or to laboratories within that country.

Three specific types of support are offered:

1. *Grants-in-aid* are designed to encourage investigations offering promise of improvement in radiological methods of diagnosis or treatment of disease. Research grants are awarded to institutions, rather than to individuals.

2. *Grants for scholars* are a transitional form of support, designed to bridge the gap between the completion of fellowship training and the period when the young scientist has thoroughly demonstrated his competence as an independent investigator. The application is submitted by the institution on behalf of the prospective scholar. If the request is approved a grant of $6000 per year will be made directly to the institution as a contribution towards the scholar's support, or his research, or both. Initial grants are limited to one year, but renewal for two additional years may be recommended.

3. *Fellowships in radiological research* are open to candidates seeking to gain research skills leading to investigative careers in the field of radiology. While persons from closely related disciplines are eligible to apply, candidates whose training has been directly in the field of radiology will receive preference under this program. Candidates must hold the M.D., Ph.D., or Sc.D. degree or the equivalent. Preference will be given to applicants who are thirty-five years of age or less.

Applications in these three categories for the fiscal year 1958-1959 should be submitted by December 1, 1957. Further details and application blanks may be obtained from the *Division of Medical Sciences – Room 309, National Academy of Sciences–National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D.C.*

The National Research Council of Canada will in the near future assume the responsibility for serving as scientific adviser to the James Picker Foundation with respect to its Canadian program.

NEW TECHNICAL DEVELOPMENT PROGRAM OF A.P.H.A.

The American Public Health Association is initiating a long-range technical development program to help communities to deal with new and changing health problems, including those of the nuclear age.

The program will concentrate initially on eight aspects of health: radiological health, accident prevention, mental health, chronic disease and rehabilitation, child health, environmental health, medical care administration and public health administration. A committee of experts in each problem will draw up statements of policy, write operating manuals, conduct field studies, surveys and demonstrations, and consult with state and local health authorities and agencies.

To co-ordinate the program a technical development board has been appointed, with Dr. Martha

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M. Eliot as chairman. Dr. Eliot was formerly chief of the United States Children's Bureau and is now professor of maternal and child health at the Harvard School of Public Health, Boston, Mass.

The technical development program is the first step in a three-year expansion and reorganization program for the American Public Health Association. The total program will require a $250,000 increase in the annual operating budget, to be reached by 1960. The Rockefeller Foundation has made a grant of $150,000 to help finance new activities during the three-year period of development.

The program was recommended by a task force of outstanding public health authorities. Their report and recommendations were adopted at the association's annual meeting in Atlantic City last November.

Among current priority health needs noted in the report are: (1) to increase the competence of individuals, families, and communities to cope with their own health problems; (2) to develop a safe environment in the home, on the road, at work and at play; (3) to extend the principles of the hygiene of housing to include adequate recreational space and special provision for such groups as children and older people; (4) to increase emphasis on air pollution abatement, stream sanitation, radiation control, and supervision of food processing methods; (5) to continually study the implications for health of such technological developments as chemical additives, agricultural changes, automation, new industrial processes, and changes in food and work patterns; (6) to maintain a full attack on the major unsolved health problems—cardiovascular diseases, mental diseases, crippling and handicapping conditions, cancer, dental diseases, diabetes and alcoholism—through prevention of occurrence or progression, early case-finding, early treatment, rehabilitation, research and training of personnel.

ESSAY CONTEST FOR MEDICAL STUDENTS

The American College of Chest Physicians is offering three cash awards for a 1958 prize essay contest, the closing date of which is April 15, 1958. The contest is open to undergraduate medical students throughout the world, and prizes will be awarded for essays on any phase of the diagnosis and treatment of chest diseases (heart and/or lungs). The first prize is $500, the second prize $300 and the third prize $200. Each winner will also receive a certificate. Further information from American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, U.S.A.

RADIOACTIVE CONTAMINATION OF PACIFIC AREAS

The United States Atomic Commission has recently put out a brochure entitled "Radioactive Contamination of Certain Areas of the Pacific from Nuclear Tests". This report, which is edited by Dr. Gordon M. Dunning, brings together the principal data on environmental contamination from the radioactive fallout following

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SQUIBB

"MYSTECLIN-V" IS A TRADEMARK

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the March 1, 1954, thermonuclear detonation at the Eniwetok Proving Ground. It collates ten radiological surveys made in the Pacific by various United States organizations, as well as the findings of American medical teams who examined exposed Marshall Islanders. The report is obtainable from the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C., at 40c a copy.

THE 1957 LONDON MEDICAL EXHIBITION

The London Medical Exhibition will take place from November 18 to 22 at the Royal Horticultural Hall, Westminster. It will be officially opened at 11:30 a.m. on November 18 by Sir Bennett Hance, Medical Adviser to the Secretary of State for Commonwealth Relations. Some 120 leading manufacturers will exhibit drugs and medical specialties; surgical, medical and hospital apparatus and instruments; technical literature and research apparatus. A number of manufacturers will, as usual, introduce new products. Many exhibitors have already indicated that information on new additions to their range will be available to visitors, and early advice includes that of several new antibiotics; new products for the treatment of epilepsy, asthma, hypertension, rheumatoid arthritis, and rhinitis; an anticoagulant for use in vascular surgery; a group of plastic materials developed for use in surgery, and new apparatus of particular value in the pulmonary field. Exhibits of medical, surgical, ophthalmological and other apparatus show an increase in number, range and interest. A program of the latest medical films will be shown throughout.

Professional men and buyers from overseas are very welcome, and invitations may be obtained by writing to: The Organizers, London Medical Exhibition, 194-200, Bishopsgate, London, E.C.2, England. Visitors without entry tickets are requested to produce professional identification.

SEROTONIN AND HISTAMINE IN MAST CELLS

The serotonin and histamine content of mast cell tumours was recently determined by a group of workers at the National Heart Institute, Bethesda, Maryland. Their studies were carried out on mice bearing solid neoplasm P185; on dogs which had a similar form of tumour although its stroma included more connective tissue than that found in mice; and finally, on two patients suffering from urticaria pigmentosa.

The mouse tumour was found to contain a very high concentration of both histamine and serotonin; the dog's tumour contained mostly histamine, as did the lesions in the two human beings. Negligible amounts of serotonin were found in the skin and bone lesions of the two patients.

It has been reported in the past that patients with carcinoid tumours produced a great deal of serotonin and histamine. Chemical analysis of three carcinoid neoplasms revealed that serotonin only was present in high titre. It is therefore presumed that the elevated histamine excretion found in the urine of these patients is probably a secondary phenomenon.—*Science*, 125: 1202, 1957.